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CONTENTS

The Effect of Streptomycin on the Emergence of Bacterial Resistance to Isoniazid. A United States Public Health Service Cooperative Investigation. 553
Pulmonary Function in Pregnancy. I. Serial Observations in Normal Women. DAVID W. CUGELL, N. ROBERT FRANK, EDWARD A. GAENSLER, AND THEODORE L. BADGER. 568
A Comparative Study of the Effectiveness of Laryngeal Swabs and Gastric Aspiration for the Detection of *M. Tuberculosis* in Chest Clinic Patients. AARON D. CHAVES, L. R. PEIZER AND D. WIDELOCK. 598
A Roentgenographic Classification of Tuberculous Lesions of the Kidney. JOHN K. LATTIMER. . 604
Tuberculous Meningitis in the Adult. A Review of Sixty Consecutive Streptomycin-Treated Cases. EDGAR ALSOP RILEY. 613
A Toxic Lipid Component of the Tubercle Bacillus ("Cord Factor"). I. Isolation from Petroleum Ether Extracts of Young Bacterial Cultures. HUBERT BLOCH, E. SORKIN, AND H. ERLENMEYER. 629
Further Observations on the Pharmacology of Isoniazid. BERNARD RUBIN AND JOHN C. BUREE. 644
The Long-Term Toxicity and Metabolic Effects of Isoniazid in Adults. EDWARD W. MULLIN, KENNETH W. WRIGHT, AND PAUL A. BUNN. 652
The Specificity of the Hemagglutinin Adsorption Technique in the Serologic Study of Tuberculosis. WILLIAM L. GABY, JOYCE BLACK, AND AMEDEO BONDI, JR. 657
Notes:
Tuberculin Patch Test Survey Among School-Age Children in Liberia. HILDRUS A. POINDEXTER. 665
Respiratory Quotients of Tubercle Bacilli at Low Oxygen Tension. JOSEPH Q. HEPLAR. . . 669
Ineffectiveness of Isoniazid and Iproniazid in Therapy of Sarcoidosis. HAROLD L. ISRAEL, MAURICE SONES, AND DICK HARRELL. 671
Preliminary Note on the Effect of Isoniazid and Iproniazid in Murine Leprosy. E. GRUNBERG AND E. H. TITSWORTH. 674
Correspondence: Tuberculosis in South America. EMIL BOGEN; Request for Reprints Concerning Stress and the Adaptive Hormones. ALEXANDER HORAVA and HANS SELYE. 676
American Trudeau Society:
The Need for Rest Therapy in Connection with Long Courses of Drug Treatment for Pulmonary Tuberculosis. A Statement by the Committee on Therapy. 679
Report of Panel Discussion on Chemotherapy in Tuberculosis. 680
Report on Team Projects for the Recovering Tuberculosis Patient in Tuberculosis Hospitals in the United States. HOLLAND HUDSON. 698
Notes. 704
Necrology. 705
Abstracts. 89

ANNUAL MEETING—LOS ANGELES, CALIF.
May 18–22, 1953

See inside back cover

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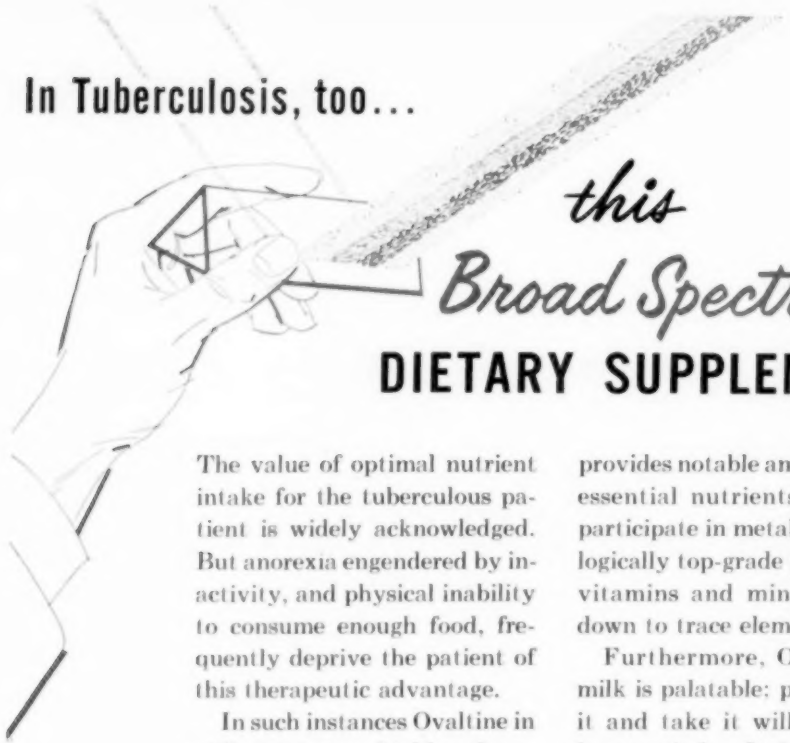

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May, 1953

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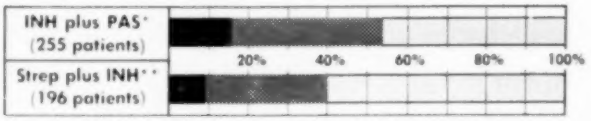
In February, a 4-day conference was held in Atlanta, Ga., attended by TB men from all parts of the country. Those present received a set of tables giving the results of various chemotherapeutic regimens as reported by 36 government hospitals. In all, 2175 patients were treated—with isoniazid alone, isoniazid and streptomycin, isoniazid and PAS, and streptomycin plus PAS.

As was expected, isoniazid alone turned out to be not as effective as *combination therapy*. The following graphs, derived from the official report, indicate some interesting results:

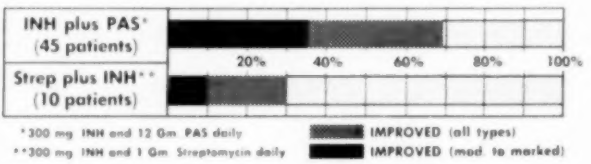
X-Ray Changes: Streptomycin-Resistant Cases

I. 2–5 MONTHS TREATMENT



When treatment is continued for more than 5 months, the results are more striking:

II. 5–10 MONTHS TREATMENT



As can be seen, the *number* of cases treated longer than 5 months is very small, and no rigorous conclusions may be drawn from the results. The data *indicates* however, that combined INH-PAS therapy may be the regimen of choice in streptomycin-resistant cases, and bear further investigation.

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THE EFFECT OF STREPTOMYCIN ON THE EMERGENCE OF BACTERIAL RESISTANCE TO ISONIAZID

A United States Public Health Service Cooperative Investigation[1]

(Received for publication February 19, 1953)

INTRODUCTION

Although its clinical significance is at present only a subject of surmise and speculation, many workers have observed the increased bacterial resistance to isoniazid which occurs in tuberculous patients treated with the drug. Interest has been widely expressed in the possibility of reducing the frequency of this occurrence by combining isoniazid with streptomycin. It therefore seems appropriate to report the early results on this point from the United States Public Health Service cooperative clinical study,[2] even though the results must be regarded as provisional and preliminary.

MATERIALS AND METHODS

In the present investigation, during each week from mid-April through August, 1952, physicians in twenty-two participating hospitals selected those patients in their hospitals whom they considered suitable for the study. According to a list of random numbers prepared in the central and coordinating office[3] of the study, each patient was assigned to one

[1] Report prepared by Shirley H. Ferebee for the following clinical investigators: Drs. F. H. Alley, E. P. Bowerman, and S. C. Carter, Tennessee State Tuberculosis sanatoriums at Memphis and Oakville, Tenn.; Dr. P. T. Chapman, Herman Kiefer Hospital, Detroit, Mich.; Dr. S. S. Cohen, Glen Lake Sanatorium, Oak Terrace, Minn.; Dr. H. G. Curtis, Sunny Acres Tuberculosis Hospital, Cleveland, Ohio; Dr. R. J. Davies, Firland Sanatorium, Seattle, Wash.; Dr. F. P. Dawson, Middlesex County Sanatorium, Waltham, Mass.; Dr. Raymond Hofstra, USPHS Hospital, Brooklyn, N. Y.; Drs. W. L. Howard and W. J. Steininger, Maybury Sanatorium, Northville, Mich.; Dr. G. E. Martin, Pittsburgh Tuberculosis Hospital, Pittsburgh, Pa.; Dr. H. M. Payne, Freedmen's Hospital, Washington, D. C.; Drs. R. F. Payne and R. F. Corpe, Battey State Hospital, Rome, Ga.; Drs. Alfred Goldman, Bernard Friedman, and M. B. Pianetto, Robert Koch Hospital, Koch, Mo.; Drs. H. C. Sweany, B. L. Brock, and W. L. Potts, Florida State sanatoriums at Orlando and Lantana, Fla.; Drs. H. S. Willis, H. F. Easom, W. H. Gentry, and C. D. Thomas, North Carolina State sanatoriums at Wilson, McCain, and Black Mountain, N. C.; Dr. G. C. Wilson, Uncas-on-Thames Sanatorium, Norwich, Conn.; and Drs. J. L. Wilson, H. C. Dooling, G. M. Eckley, and H. W. Weest, Pennsylvania State sanatoriums at South Mountain, Cresson, and Hamburg, Pa.

[2] The isoniazid for this study was generously supplied by E. R. Squibb & Sons as Nydrazid.

[3] Field Research Branch, Division of Chronic Disease and Tuberculosis, Public Health Service, Federal Security Agency.

of the three following regimens: streptomycin plus para-aminosalicylic acid (PAS), streptomycin plus isoniazid, and isoniazid alone. Streptomycin was given in dosages of 1 gm. twice a week, PAS 10 to 12 gm. daily, and isoniazid 150 to 300 mg. daily. The protocol provides for a 64-week period of observation: a 40-week control period, during which only the chemotherapy determined by chance is used; and a 24-week post-treatment observation period. By September, 1952, 1,500 cases were under observation.

For the purpose of obtaining uniformity in the determination of the drug susceptibility of the tubercle bacilli, arrangements were made to have cultures from all of the twenty-two cooperating hospitals tested in a single central laboratory (the Trudeau Laboratory, under the supervision of Mr. William Steenken, Jr.).

Limitations of space and personnel made it impossible to test at frequent intervals all positive cultures from 1,500 patients. Therefore a plan was adopted whereby cultures planted at the beginning and after 40 weeks of treatment would be sent to the Trudeau Laboratory for all patients in all hospitals. Information on changes during treatment was to be obtained by testing all cultures of *M. tuberculosis* obtained at four-week intervals from all patients in five of the twenty-two hospitals.

Drug-susceptibility determinations were performed in the following manner:

> Each culture was tested in the Trudeau Laboratory for susceptibility to isoniazid and to streptomycin without knowledge of the patient's therapy, clinical condition, or previous test results. A representative sample of the entire bacterial population of the specimen, equivalent in size to that of several full-grown colonies, was transferred by means of a platinum spade to a tube containing 5 ml. of Tween[1]-albumin liquid medium. The transfer was effected by triturating the organisms against the side of the tube until a homogeneous suspension was obtained and then incubating the culture at 37.5°C. until a standard degree of turbidity was obtained, usually in 10 to 14 days. At that time, slants of solid Steenken and Smith medium were inoculated by distributing one double loopful of the liquid medium culture evenly over the entire surface of each slant in a 20- by 140-mm. test tube. For each test, a minimum of six slants were used: one control tube without drug; and tubes containing each of the following concentrations of drugs per ml.: streptomycin, 10 and 100 γ; isoniazid, 0.1, 1.0, and 5.0 γ. Cultures showing significant growth in 5.0 γ of isoniazid were also planted in concentrations of 10 and 25 γ per ml. Each tube was observed, always by the same person, at the end of the second, third, fourth, fifth, and sixth weeks of incubation, and the amount of growth was recorded in one of the following categories: actual colony count if less than 50; 1+ = 50 to 200 colonies; 2+ = more than 200 colonies but not uncountable; 3+ = innumerable but not confluent colonies; 4+ = confluent growth over the entire surface.

For the results reported here, at least 3-plus growth at 5 weeks has been required in the control tube for both streptomycin- and isoniazid-susceptibility determinations. Organisms have been considered resistant to streptomycin if at least 3-plus growth occurred within 5 weeks in the 10 γ per ml. concentration of streptomycin.

Experience with isoniazid is at present much too limited to establish a meaningful dichotomy between isoniazid-resistant and isoniazid-susceptible organisms, either with respect to the critical concentration or the amount of growth. While it is probable that one may safely characterize one end of the scale as sensitive

[1] Tween 80 is the proprietary name for the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

and the other as resistant, the determination of a point which represents a change in the character of the bacterial population *of significance in terms of drug neutralization* must await correlation with clinical and roentgenographic data.

At present, therefore, it is possible only to designate arbitrarily a certain amount of growth as a standard and to report the frequency with which that amount of growth appears in the various concentrations of isoniazid without reference to the clinical aspects of the problem.

Inspection of the data revealed growth of less than 50 colonies in 0.1 γ of isoniazid per ml. in a few pretreatment cultures, but none showed growth greater than 50 colonies in 0.1 γ or any growth in higher concentrations. For measuring the effect of treatment on the character of the bacterial population, it seems appropriate to consider as "no growth" levels which may be detected without treatment. Accordingly, for the present analysis, inoculated cultures reported as showing "growth" contained at least 50 colonies (1 plus) after 5 weeks of incubation.

A study of 1,500 patients should yield a fairly large amount of data on bacterial drug susceptibility. A combination of factors, however, has reduced considerably the material available for analysis at the present time.

> First, it was necessary to limit to five the number of hospitals from which cultures would be tested each month. Actually, tests from only four centers are used since unforeseen difficulties in the laboratory of one hospital made it impossible to prepare the necessary cultures to send to the central laboratory. Second, patients entering the study late in the summer are not included because there has not yet been time to accumulate both a suitable period of observation during treatment *and* the 12-week period needed for the laboratory work (6 weeks for growth of the original culture in the hospital laboratory plus 6 weeks for sensitivity tests in the central laboratory). Despite these limitations, 265 patients entered the study early enough for bacillary drug-susceptibility tests to have been completed during 28 weeks of treatment.

Not all of this base population of 265 patients, however, furnish data for the study of drug resistance. Cultures negative for tubercle bacilli were obtained from 78 patients during the week before treatment was begun, thus reducing the number with positive pretreatment cultures to 187. And in this latter group, 37 patients were lost from observation, most of them because they left the hospital against medical advice. There remain, as shown in table 1, 150 patients who form the basis for a preliminary report on the effect of therapy and the emergence of drug-resistant organisms.

Study of the records of the total group of 187 patients does not indicate that a serious bias was introduced by excluding from the analysis the 37 patients for whom treatment was interrupted.

The details of the patient population from which this material is drawn may be seen in table 1.

It is believed that results based on only the 150 patients, all of whom had been observed for the same length of time, are much to be preferred to observations on the larger number which might have been obtained by including patients who had been observed for different, and shorter, intervals of time.

The basic data for the report are summarized in tables 2 and 3. Table 2 specifically deals with the results of testing for isoniazid resistance and includes the

TABLE 1

PATIENT POPULATION FORMING BASIS OF BACTERIOLOGIC STUDIES

PRETREATMENT STATUS	TOTAL	ISONIAZID	STREPTOMYCIN PLUS ISONIAZID	STREPTOMYCIN PLUS PARA-AMINOSALICYLIC ACID
Patients observed 28 weeks	265	92	89	84
Culture negative for *M. tuberculosis* on entry	78	30	27	21
Culture positive for *M. tuberculosis* on entry	187	62	62	63
Treatment interrupted	37	7	12	18
Treatment continuous	150	55	50	45
Streptomycin-resistant	56	19	22	15
Streptomycin-susceptible	94	36	28	30

TABLE 2

RESULTS OF CULTURE EXAMINATION OF SPUTUM AND ISONIAZID-SUSCEPTIBILITY TESTS OF PATIENTS WITH POSITIVE CULTURES AT START OF TREATMENT

TREATMENT REGIMEN	WEEKS OF TREATMENT							
	0	4	8	12	16	20	24	28
Isoniazid								
Total	55	55	55	55	55	55	55	55
Positive	55	40	34	30	32	36	30	27
Growth in 5.0γ	—	2	8	10	12	15	15	14
Growth in 1.0γ	—	—	6	10	10	9	7	9
Growth in 0.1γ	—	1	7	7	9	10	8	4
No growth at 0.1γ	55	37	13	3	1	2	—	—
Negative	—	15	20	23	23	18	22	26
Pending	—	—	1	2	—	1	3	2
Streptomycin plus isoniazid								
Total	50	50	50	50	50	50	50	50
Positive	50	32	27	19	14	11	15	12
Growth in 5.0γ	—	—	2	3	6	7	7	7
Growth in 1.0γ	—	—	2	1	—	1	2	1
Growth in 0.1γ	—	2	6	6	7	3	5	4
No growth at 0.1γ	50	30	17	9	1	—	1	—
Negative	—	17	23	30	36	37	33	31
Pending	—	1	—	1	—	2	2	7
Streptomycin plus PAS								
Total	45	45	45	45	45	45	45	45
Positive	45	31	28	23	23	22	19	16
Negative	—	14	17	22	22	23	23	25
Pending	—	—	—	—	—	—	3	4

laboratory observations on all 150 patients; table 3 deals with resistance to streptomycin and includes observations for only the 94 patients who did not

already harbor organisms resistant to streptomycin when they were entered in the study. Both tables show, at each 4-week interval for 28 weeks, the number of patients whose cultures were reported as pending (laboratory work incomplete), negative, and positive for tubercle bacilli; and, for the positive cultures, the concentration of drug in which the organisms grew.

TABLE 3

RESULTS OF CULTURE EXAMINATION OF SPUTUM AND STREPTOMYCIN-SUSCEPTIBILITY TESTS OF PATIENTS WITH STREPTOMYCIN-SUSCEPTIBLE CULTURES AT START OF TREATMENT

TREATMENT REGIMEN	WEEKS OF TREATMENT							
	0	4	8	12	16	20	24	28
Isoniazid								
Total	36	36	36	36	36	36	36	36
Positive	36	26	21	17	18	21	16	15
Negative	—	10	14	18	18	15	17	19
Pending	—	—	1	1	—	—	3	2
Streptomycin plus isoniazid								
Total	28	28	28	28	28	28	28	28
Positive	28	19	13	8	5	3	4	3
Growth in 100γ	—	—	—	1	2	2	2	2
Growth in 10γ	—	2	1	1	1	—	1	1
No growth in 10γ	28	17	12	6	2	1	1	—
Negative	—	8	15	19	23	24	23	21
Pending	—	1	—	1	—	1	1	4
Streptomycin plus PAS								
Total	30	30	30	30	30	30	30	30
Positive	30	19	16	12	12	13	10	8
Growth in 100γ	—	—	1	1	3	2	2	2
Growth in 10γ	—	3	1	3	1	4	5	5
No growth in 10γ	30	16	14	8	8	7	3	1
Negative	—	11	14	18	18	17	18	19
Pending	—	—	—	—	—	—	2	3

RESULTS

Bacterial Content of Sputum

Figure 1 shows graphically how the three treatment regimens compare with respect to the proportion of patients whose cultures were positive for tubercle bacilli during 28 weeks of treatment. The upper half of the page shows the trends for all patients with initially positive cultures. The differences among the three groups are slight through the twelfth week of treatment, when the percentage of positive cultures continues sharply downward among streptomycin-isoniazid patients but remains practically unchanged in the streptomycin plus PAS and the isoniazid groups. At the twenty-eighth week, tubercle bacilli were detected in the cultures of 24 per cent of the streptomycin-isoniazid patients, 36 per cent of the streptomycin-PAS patients, and 49 per cent of the isoniazid patients. It may be seen that, although the differences are sometimes small, the propor-

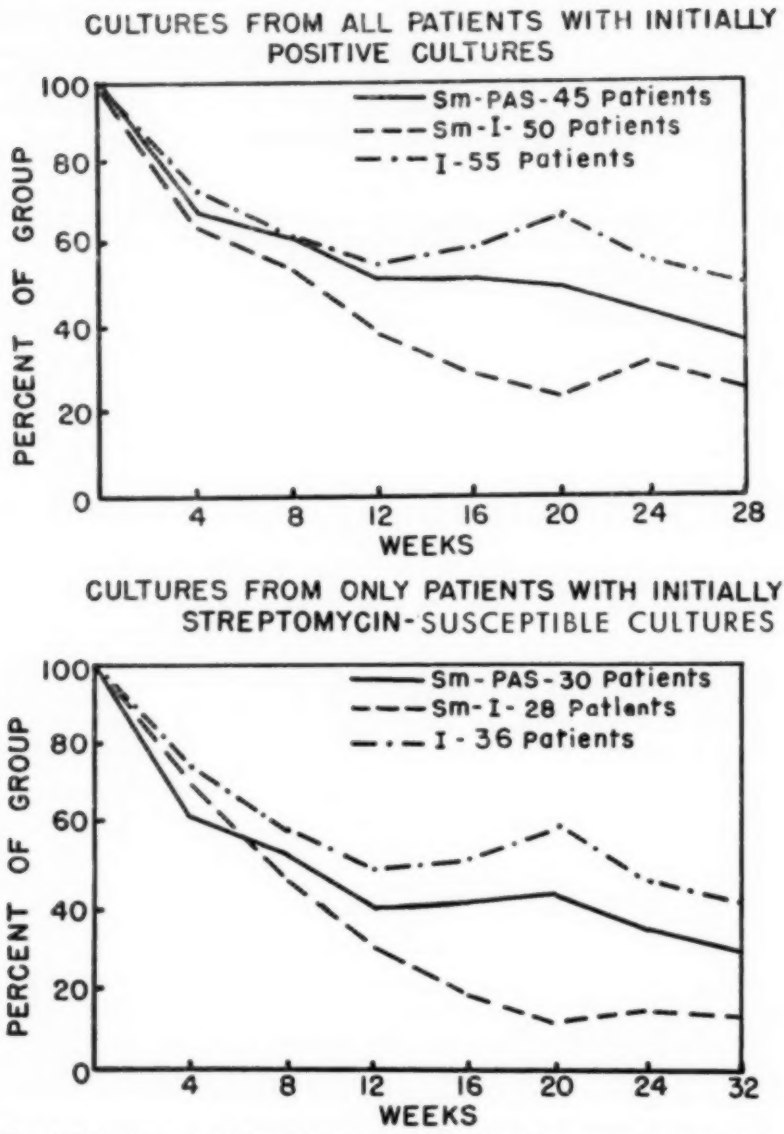

FIG. 1. Frequency of positive cultures during 28 weeks of treatment among patients with initially positive cultures.

tion is always lowest in the streptomycin-isoniazid group, second in the streptomycin-PAS group, and highest in the isoniazid group.

In the lower half of figure 1, similar data are presented for patients with streptomycin-susceptible organisms at the start of treatment. While the order of rank of the three regimens is the same as for the total group shown in the upper half of figure 1, the decrease in the proportion of positive cultures during treatment is greater on all regimens among the patients with streptomycin-susceptible tubercle bacilli. At the end of 28 weeks of treatment, the proportion of positive cultures had decreased to 11 per cent with the use of streptomycin plus isoniazid, 27 per cent with streptomycin plus PAS, and 42 per cent with isoniazid.

Isoniazid Susceptibility

In figure 2, the results of culture examinations and isoniazid-susceptibility tests are compared graphically for 50 patients receiving streptomycin plus isoniazid and for 55 patients receiving isoniazid. Although it would have been desirable to have restricted the analysis to only the patients with streptomycin-susceptible infections at the start of the study, the size of the material made this impracticable.

After 12 weeks of therapy with isoniazid alone, there is little further decrease through 28 weeks in the frequency of positive cultures. At this point, when half of the cultures have become negative and half have remained positive, most of the positive cultures have acquired some capacity to grow in isoniazid. During the remaining 16 weeks of observation there is evidence of a shift in the degree of susceptibility to isoniazid. At 12 weeks, 13, 18, and 18 per cent of the total cultures showed growth in the 0.1, 1.0, and 5.0 γ concentrations of isoniazid, respectively, while at 28 weeks these proportions had shifted to 7, 16, and 25 per cent.

Patients treated with streptomycin and isoniazid differed from those who received isoniazid alone, as shown in the upper section of figure 2. The point in time at which there is no further reduction in the frequency of positive cultures (the same point at which all positive cultures show growth in isoniazid) is advanced to the sixteenth or perhaps even to the twentieth week in the group which received both drugs. Regarded from another viewpoint, it can be said that combining both drugs delays the time of disappearance of cultures having isoniazid-susceptible organisms. The clinical significance of this delay is that, with isoniazid alone, approximately half of the patients continue to show tubercle bacilli in their sputum, while, with both drugs, only approximately one-quarter continue to have positive cultures. The group in which 1.0 γ was the highest concentration with 1-plus growth was small (4 per cent) in comparison with both the 0.1 γ and 5.0 γ groups. The proportion of patients whose cultures showed growth at the 5.0 γ level reached a peak of 14 per cent at 20 weeks which was maintained during the next 8 weeks of treatment. By the twenty-eighth week, all cultures remaining positive exhibited growth in some concentration of isoniazid.

From the above presentation it must be clear that the problems of drug resistance cannot be confined, as is often done, to an analysis of the group of patients who continue to discharge tubercle bacilli, disregarding the obvious

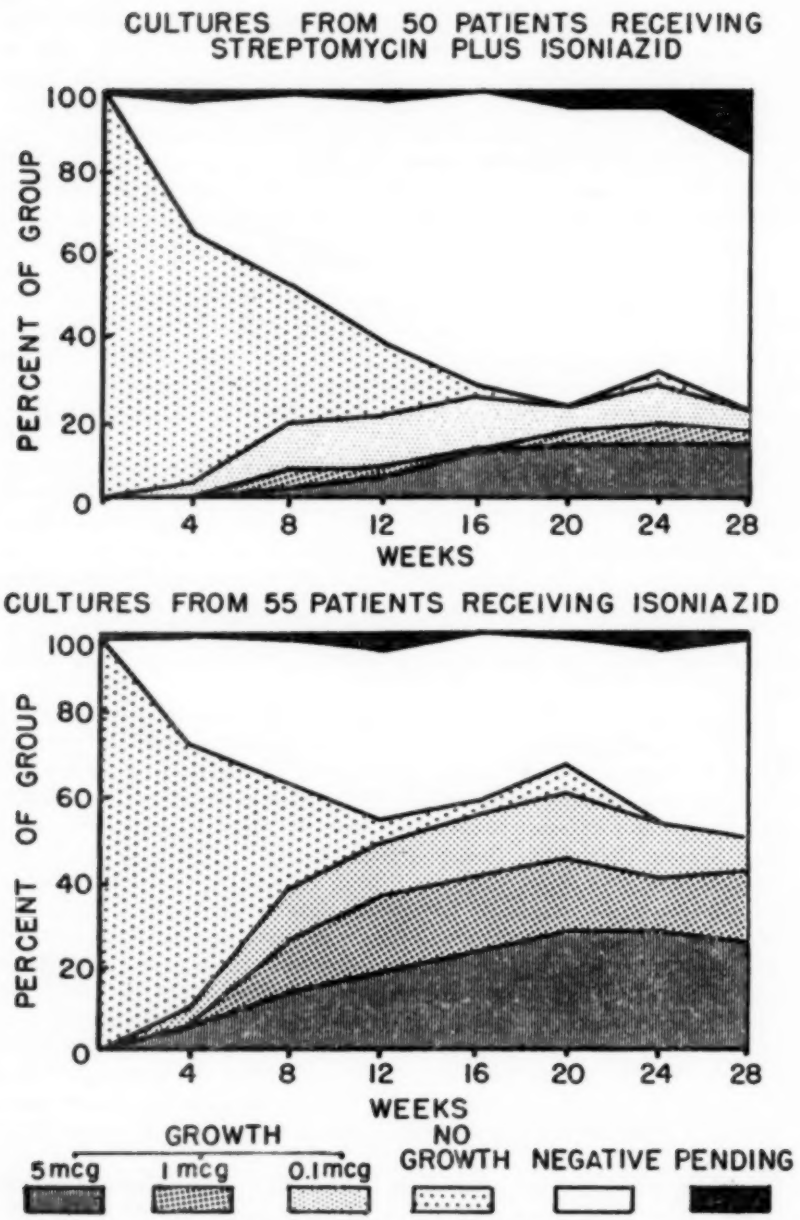

FIG. 2. Results of culture examinations and isoniazid-susceptibility tests

significance of the size and characteristics of the group in which the cultures become negative. The pitfalls of neglecting the negative group can be illustrated in table 4 (derived from table 2).

If only the positive cultures were considered, isoniazid alone would have equal merit, or rather lack of merit, with streptomycin plus isoniazid with respect to isoniazid susceptibility. Growth in 5.0 γ would be charged to more than half on each regimen, and growth in at least 0.1 γ would be attributed to 100 per cent of each. Such an approach completely obscures the critical point: that among a given number of patients, resistance to isoniazid will appear much less frequently if the patients are treated with both drugs.

Isoniazid Susceptibility Related to Pretreatment Status

In table 5 information is given on the significance of cavities and of susceptibility to streptomycin at the beginning of treatment in relation to the laboratory findings after 28 weeks of therapy. The number of cases in each subgroup is

TABLE 4

ISONIAZID SUSCEPTIBILITY AFTER 28 WEEKS OF TREATMENT

	NUMBER		PER CENT OF PATIENTS		PER CENT OF POSITIVE CULTURES	
	Streptomycin plus Isoniazid	Isoniazid	Streptomycin plus Isoniazid	Isoniazid	Streptomycin plus Isoniazid	Isoniazid
Patients	50	55	100.0	100.0		
Cultures positive for *M. tuberculosis*	12	27	24.0	49.1	100.0	100.0
Growth in 5.0γ	7	14	14.0	25.4	58.4	51.9
Growth in 1.0γ	1	9	2.0	16.4	8.3	33.3
Growth in 0.1γ	4	4	8.0	7.3	33.3	14.8
Growth in at least 0.1γ	12	27	24.0	49.1	100.0	100.0

obviously small but the results suggest that important differences in the effect of treatment are related both to the extent of disease and to previous drug therapy.

Among 24 patients without cavities, only 3 (just more than 10 per cent) still have cultures positive for tubercle bacilli after 28 weeks of treatment with isoniazid or isoniazid and streptomycin. Among 81 patients with cavities, 36 (nearly 50 per cent) have positive cultures. Patients who both have cavities and harbor streptomycin-resistant organisms benefited still less from treatment; of 35 patients, 20 (nearly 60 per cent) failed to show "conversion" from a positive to a negative culture.

These findings in relation to streptomycin resistance at the beginning of treatment should not be interpreted too literally as reflecting an effect of streptomycin resistance per se. Because it is one characteristic which can be measured, streptomycin resistance becomes a convenient label to place on a group of patients who in the main have had their disease for a considerable period of time and

have received streptomycin therapy with results inconclusive enough to require further chemotherapy as evidenced by their availability for this study.

Streptomycin Susceptibility

The emergence of streptomycin-resistant organisms when streptomycin is used with isoniazid and with PAS has been examined in patients whose pretreatment cultures were susceptible to streptomycin. The basic data in table 3 supply the material for figure 3, which shows graphically the results of culture examinations and streptomycin-susceptibility tests among 28 patients who received streptomycin plus isoniazid and among 30 patients who received streptomycin plus PAS for 28 weeks.

When isoniazid was used with streptomycin, the proportion of positive cultures declined very rapidly until the twentieth week, when only 11 per cent of the

TABLE 5

PRETREATMENT STATUS RELATED TO CULTURE RESULTS AND ISONIAZID SUSCEPTIBILITY AT 28 WEEKS

CULTURE RESULTS AND ISONIAZID SUSCEPTIBILITY AT 28 WEEKS	ISONIAZID PATIENTS					SM-ISONIAZID PATIENTS				
		Without Cavity		With Cavity			Without Cavity		With Cavity	
	Total	SM-S	SM-R	SM-S	SM-R	Total	SM-S	SM-R	SM-S	SM-R
Total	55	10	4	26	15	50	8	2	20	20
Positive	27	2	1	13	11	12	—	—	3	9
Growth in 5.0γ	14	1	1	5	7	7	—	—	1	6
Growth in 1.0γ	9	1	—	5	3	1	—	—	1	—
Growth in 0.1γ	4	—	—	3	1	4	—	—	1	3
No growth in 0.1γ	—	—	—	—	—	—	—	—	—	—
Negative	26	8	3	11	4	31	7	2	14	8
Pending	2	—	—	2	—	7	1	—	3	3

SM-S = streptomycin-susceptible.
SM-R = streptomycin-resistant.

cultures were positive for tubercle bacilli, and remained at about this level through the twenty-eighth week. In the fourth week, 7 per cent of the cultures showed resistance in the 10 γ concentration of streptomycin but the proportion never rose above 4 per cent thereafter. Growth in the 100 γ concentration first appeared in the twelfth week of treatment and stayed at 7.1 per cent from the sixteenth through the twenty-eighth weeks.

When patients were treated with PAS plus streptomycin, the decline in the proportion of cultures positive for tubercle bacilli was less marked, reaching a level of 40 per cent in the twelfth week and fluctuating only slightly through the twenty-eighth week. Growth in the 10 γ concentration appeared during the fourth week of treatment in 10 per cent of the cultures and with minor variations had reached 17 per cent in the twenty-eighth week. Organisms resistant to 100 γ of streptomycin were detected in the eighth week of treatment and by the twenty-eighth week were present in 7 per cent of the cultures.

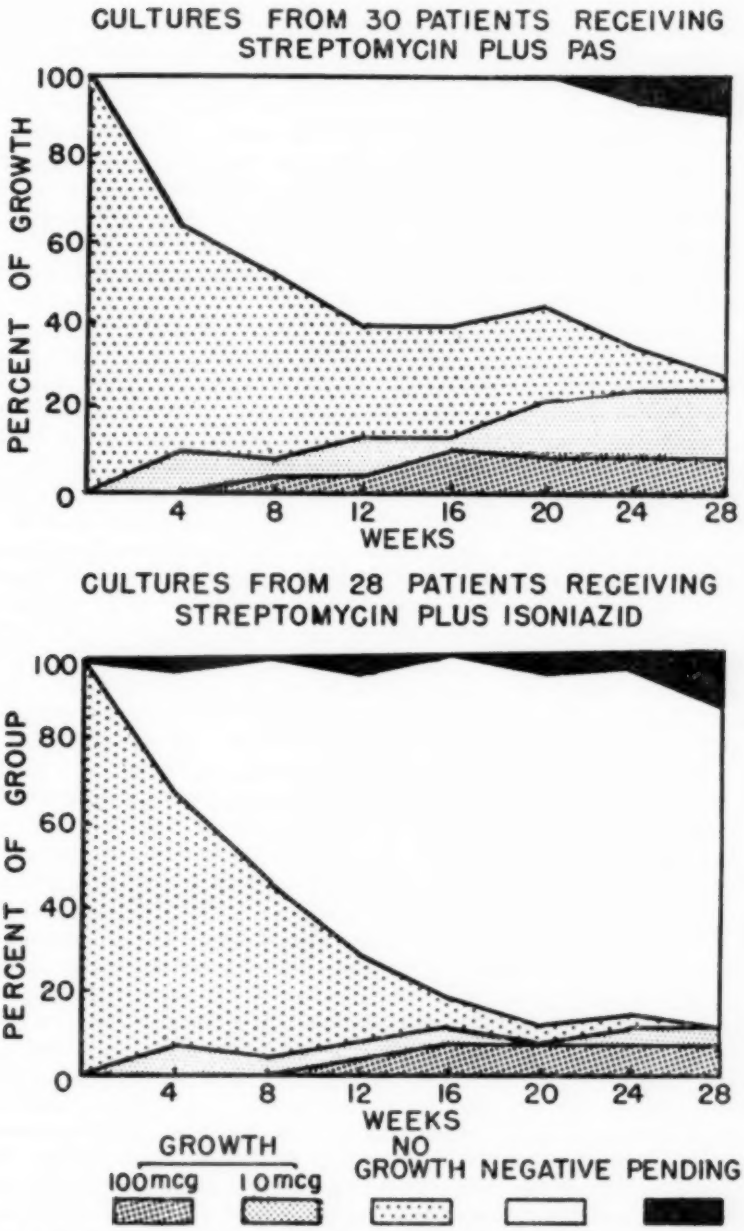

FIG. 3. Results of culture examinations and streptomycin-susceptibility tests

The results on the two regimens are very similar in two respects: 7 per cent of the cultures displayed streptomycin resistance in the 100 γ concentration from the twelfth through the twenty-eighth weeks; by the twenty-eighth week practically no cultures wholly sensitive to streptomycin remained in either group.

The main difference between the two regimens seems to be that isoniazid is specifically more effective than PAS in preventing the emergence of organisms which are only moderately susceptible to streptomycin. The significant effect of this difference is that, when isoniazid is combined with streptomycin, approximately one patient in 10 still has tubercle bacilli in his sputum after 28 weeks of treatment; when PAS is combined with streptomycin, approximately 3 patients in 10 still have cultures positive for *M. tuberculosis*.

DISCUSSION

Preliminary bacteriologic results from a large-scale clinical trial are given for the first 150 tuberculous patients treated for 28 weeks with isoniazid alone, isoniazid combined with streptomycin, and streptomycin combined with PAS. Tubercle bacilli able to grow in various concentrations of isoniazid appear within a few months in almost all patients *who fail during treatment to become bacteriologically negative for tubercle bacilli*. This seems to be true whether isoniazid is given alone or in combination with streptomycin. Moreover, when streptomycin and isoniazid are used together, all of the cultures continuing to be positive after 28 weeks of treatment are *resistant to both drugs*. It is not possible at present to interpret this "dual resistance" in terms of drug neutralization in patients. Nevertheless, until more precise information is available, the possible implications of the phenomenon must be taken into consideration in clinical practice. But the significance of having drug-resistant organisms must be judged in relation to the frequency with which treatment effects an even more important factor, the disappearance of bacilli from the patient's sputum.

On all three treatment regimens a high proportion of the patients become bacteriologically "negative," isoniazid with streptomycin being the most, and isoniazid alone the least, effective in this respect. The absolute percentage of a group of patients that become "negative," or remain "positive," apparently depends to a considerable extent on such factors as severity of the disease and previous antimicrobial treatment. The presence of cavities, for example, tends to reduce a patient's chances of becoming bacteriologically "negative" and, therefore, increases his chances of completing a course of isoniazid therapy with tubercle bacilli still in his sputum and with those organisms resistant to isoniazid.

Several circumstances dictate a fair measure of caution in the interpretation of these results. First, there is as yet little direct evidence on the clinical significance of enhanced growth of tubercle bacilli in various concentrations of isoniazid. Indirect evidence of its lack of significance is provided by the continuous improvement observed in patients considerably beyond the sixteenth week when these results indicate that some degree of resistance has been acquired in practically all of the cultures still positive for tubercle bacilli. Second, the material yet available for analysis is very small and the results are consequently subject to a large random variation. Third, culture examinations and tests of bacterial

drug susceptibility are undoubtedly subject to large experimental errors. Fourth, the arbitrary standard of 1-plus growth adopted for isoniazid susceptibility tests in this first analysis of the material may well prove to require revision.

SUMMARY

In a large-scale clinical trial, patients have been subdivided by random allocation into three treatment groups receiving isoniazid, streptomycin plus isoniazid, and streptomycin plus para-aminosalicylic acid (PAS). At this time, preliminary data on the results of culture examinations and tests of bacterial susceptibility are reported for 150 patients, all of whom have been treated for 28 weeks.

Isoniazid susceptibility has been determined for the cultures of tubercle bacilli from the patients who received isoniazid alone or in combination with streptomycin, and streptomycin susceptibility for the organisms cultured from the patients who received streptomycin in combination with isoniazid or with PAS. The tests were carried out in one laboratory without knowledge of the patient's clinical condition, therapy, or previous results. Among cultures that were still "positive" after 28 weeks of treatment: practically all showed some resistance to isoniazid when patients received isoniazid alone; nearly all showed resistance of some degree to both streptomycin and isoniazid when patients were treated with both drugs; and all were at least moderately resistant to streptomycin when patients received streptomycin and PAS.

In brief, all cultures positive for *M. tuberculosis* obtained after 28 weeks of treatment with any of these drug combinations contained tubercle bacilli which had lost some measure of their initial susceptibility to the particular drugs (excluding PAS) to which they had been exposed.

In another and more critical respect, however, the three treatment regimens are not equal. After 28 weeks of treatment, tubercle bacilli were detected in the cultures of one-half of the isoniazid patients, one-third of the streptomycin-PAS patients, and one-fourth of the streptomycin-isoniazid patients. Thus, while all "positive" cultures of all patients treated with any of the three regimens contained organisms resistant to the drugs given, substantially fewer patients continued to have cultures positive for tubercle bacilli after treatment with the combination of streptomycin and isoniazid.

In the management of tuberculous patients, these regimens offer no easy choice for the clinician. The regimen which offers the greatest probability of "negative" sputum provides also the near certainty of bacilli resistant to both streptomycin and isoniazid if the sputum has not become free of tubercle bacilli. The other two regimens which offer less chance of sputum conversion will, on the other hand, produce bacilli resistant to only one of the potent drugs, leaving either streptomycin or isoniazid for subsequent use.

SUMARIO

El Efecto de la Estreptomicina sobre la Formación de Resistencia Bacteriana a la Isoniacida

En un ensayo clínico en gran escala, se subdividió a los enfermos al azar en tres grupos terapéuticos que recibieron, respectivamente, isoniacida, estreptomicina más isoniacida y

estreptomicina más ácido para-aminosalicílico (PAS). Preséntanse ahora datos preliminares sobre los resultados de los exámenes de los cultivos y las pruebas de la sensibilidad bacteriana en 150 enfermos, todos ellos tratados durante 28 semanas.

La sensibilidad a la isoniacida fué determinada en los cultivos positivos para el *M. tuberculosis* de los sujetos que recibieron isoniacida ya sola o combinada con estreptomicina y la sensibilidad a la estreptomicina en los cultivos de los que recibieron estreptomicina combinada con isoniacida o con PAS. Las pruebas fueron ejecutadas en un laboratorio que no conocía el estado clínico del enfermo, la terapéutica o los resultados obtenidos anteriormente. Entre los cultivos que eran todavía positivos al cabo de 28 semanas de tratamiento: casi todos mostraron alguna resistencia a la isoniacida cuando los enfermos recibían esa droga sola; casi todos revelaron alguna resistencia tanto a la estreptomicina cuanto a la isoniacida cuando los enfermos eran tratados con ambas; y todos ofrecían a lo menos moderada resistencia a la estreptomicina cuando los sujetos recibían esa droga y PAS.

En resumen, todos los cultivos positivos para el *M. tuberculosis*, obtenidos al cabo de 28 semanas de tratamiento con cualquiera de esas combinaciones medicamentosas contenían bacilos tuberculosos que habían perdido parte de su susceptibilidad inicial a las drogas dadas (excluyendo el PAS) a las que habían estado expuestos.

Sin embargo, en otro y más importante sentido, no son iguales los tres regímenes terapéuticos. Después de 28 semanas de tratamiento, se descubrieron bacilos tuberculosos en los cultivos de la mitad de los tratados con isoniacida, la tercera parte de los tratados con estreptomicina-PAS y la cuarta parte de los tratados con estreptomicina-isoniacida. Así pues, aunque todos los cultivos positivos de todos los enfermos tratados con cualquiera de los tres regímenes contenían microbios resistentes a las drogas administradas, un número substancialmente menor continuó mostrando cultivos positivos después del tratamiento con la combinación de estreptomicina e isoniacida.

En las asistencia de los tuberculosos, esos regímenes no ofrecen fácil elección al clínico. El régimen que ofrece más probabilidades de obtener un esputo negativo también contiene la cuasicerteza de que habrá bacilos resistentes tanto a la estreptomicina como a la isoniacida si el esputo no ha quedado exento de bacilos tuberculosos. En cambio, los otros regímenes que ofrecen menos probabilidades de viraje del esputo producen bacilos resistentes a una sola de las drogas potentes, dejando así disponible en reserva ya la estreptomicina o la isoniacida.

RESUME

L'action de la streptomycine sur l'apparition de la résistance bactérienne a l'isoniazide

Dans une expérimentation clinique étendue, les malades ont été répartis au hasard en trois groupes qui ont été traités respectivement avec de l'isoniazide, de la streptomycine plus de l'isoniazide, de la streptomycine plus de l'acide para-aminosalicylique (PAS). L'auteur communique les données préliminaires obtenues à ce jour, à la suite de l'examen des cultures et des tests de sensibilité bactérienne chez 150 malades, tous ayant été traités pendant 28 semaines.

La sensibilité à l'isoniazide a été déterminée pour des cultures positives pour le *M. tuberculosis*, provenant de malades traités par l'isoniazide seule ou associée à la streptomycine, ainsi que la sensibilité à la streptomycine des cultures de ceux recevant la streptomycine associée à l'isoniazide ou au PAS. Les tests ont été effectués dans un laboratoire dépourvu d'informations sur l'état clinique du malade, le traitement ou les résultats antérieurs. Parmi les cultures qui étaient encore positives au bout de 28 semaines de traitement, pratiquement toutes montraient une certaine résistance à l'isoniazide quand l'isoniazide était administrée seule; presque toutes montraient un certain degré de résistance à la fois pour la streptomycine et pour l'isoniazide quand les deux antibiotiques étaient administrés; toutes montraient un degré modéré de résistance à la streptomycine quand les malades recevaient la streptomycine et le PAS.

En résumé, toutes les cultures positivés pour le *M. tuberculosis*, ayant été obtenues au bout de 28 semaines de traitement avec l'un ou l'autre de ces combinaisons d'antibiotiques,

contenaient des bacilles tuberculeux ayant perdu une partie de leur sensibilité initiale à la substance particulière (sauf le PAS) à laquelle ils avaient été exposés.

Cependant, à un autre et plus important point de vue, les trois sortes de traitements n'ont pas une valeur égale. Au bout de 28 semaines de traitement, des bacilles tuberculeux ont été décelés dans les cultures chez la moitié des malades traités par l'isoniazide, chez un tiers des malades recevant l'association streptomycine-PAS et chez un quart des malades traités par la streptomycine-isoniazide. Ainsi, tandis que toutes les cultures positives de tous les malades traités avec l'un quelconque des trois antibiotiques contenaient des germes résistants aux substances administrées, le nombre des malades dont les cultures demeuraient positives après le traitement avec la streptomycine et l'isoniazide était nettement plus bas.

Dans le traitement du tuberculeux, le choix entre ces médications n'est pas facile pour le clinicien. La médication qui offre le plus de chance d'obtenir des crachats négatifs est aussi celle qui amène la presque certitude de voir apparaître des bacilles résistants à la streptomycine et à l'isoniazide lorsque les crachats ne sont pas débarrassés du bacille tuberculeux. D'autre part, avec les deux autres modes de traitement, qui offrent moins de chance de conversion des crachats, la production de bacilles résistants est limitée à un seul des antibiotiques actifs, il subsiste en réserve soit la streptomycine soit l'isoniazide.

PULMONARY FUNCTION IN PREGNANCY[1,2,3]

I. Serial Observations in Normal Women

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INTRODUCTION

Numerous clinical studies have been made to appraise the influence of pregnancy on the course of pulmonary tuberculosis. At present it is thought that intercurrent pregnancy has little effect on the ultimate prognosis, which appears to depend more on native resistance and the type of tuberculosis present (1–6). Accepting this premise, it is nevertheless difficult to overlook the frequent, temporary improvement during pregnancy or the exacerbations of pulmonary disease so often seen following delivery. It has been repeatedly suggested that amelioration of symptoms and diminution in size of cavities during pregnancy are due to pulmonary collapse brought about by increasing intra-abdominal pressure and elevation of the diaphragm. Conversely, extension of disease after delivery has been ascribed to a sudden increase of lung volume (7–19). On the basis of these clinical observations, the use of abdominal binders (8, 9), artificial pneumothorax (5, 8, 17, 18), pneumoperitoneum (16), and collapse by thoracoplasty (16, 18) has been suggested during or immediately after pregnancy for women with active tuberculosis.

Clinical reports dealing with the course of tuberculosis during pregnancy have not been supplemented by physiologic measurements of pulmonary volumina or breathing capacity, nor have the pulmonary functional alterations observed after therapeutic collapse measures been compared with changes occurring during pregnancy. Quantitative studies, comparing the effect of pregnancy with therapeutic collapse, have been limited to fluoroscopic and roentgenographic measurements of the level and range of motion of the diaphragm and thoracic cage (20–22).

The present study of the ventilatory function at intervals during and after pregnancy was undertaken:

(*1*) to quantitate the changes in lung volumes and hence the "collapse" caused by the pregnant uterus;

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[2] This investigation was supported, in part, by research grants from the National Institutes of Health, Public Health Service; and from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] Presented in part before the Medical Session, as part of the *Medical Session on Tuberculosis*, at the annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 27, 1952.

(*2*) to study certain aspects of pulmonary function, particularly the maximum breathing capacity and the intrapulmonary mixing index, not previously measured during pregnancy;

(*3*) to ascertain the additional demands on the respiratory apparatus made by pregnancy; and

(*4*) to correlate the subjective complaint of dyspnea during pregnancy with objective measurements of altered breathing reserve.

Pneumoperitoneum, among all the collapse measures, most closely resembles pregnancy in its effect on the respiratory apparatus. In the second paper of this series, the physiologic consequences of pneumoperitoneum, observed in young women with pulmonary tuberculosis and "functionally normal" lungs, will be compared to the ventilatory changes encountered during pregnancy (23). Studies will also be reported of women with pulmonary tuberculosis who were observed throughout pregnancy and in whom pneumoperitoneum was induced in the early postpartum period. Finally, functional alterations during pregnancy in patients with pulmonary insufficiency will be reported in the third paper of this series (24).

REVIEW OF LITERATURE

Most previous observations of pulmonary function during pregnancy have been limited to measurement of the vital capacity. The earliest studies showed no striking changes (25, 26). Investigations since then have led to reports of increased (27–33), unaltered (34, 35), or decreased (36–38) vital capacity during the later months of pregnancy. Nevertheless, there has been agreement in two respects: Changes, when they did occur, were never large and, in different persons studied by the same observers, there were variations not only in magnitude but even in direction of these changes. Often, only a small number of patients were investigated, and usually the volumes of the vital capacity in pregnant women at term were compared with normal standards derived from different subjects. Thomson and Cohen (32) have pointed out that every careful study based on repeated observations of the same patients has shown a tendency toward increase of the vital capacity during pregnancy and a slight decrease after delivery. This was supported by their own findings in thirty-one normal pregnant women in whom the mean vital capacity rose from 3,260 cc. in the twenty-first week to 3,450 cc. in the fortieth week and dropped to 3,150 cc. three to six weeks after delivery. Similar changes were reported by Widlund (33). His "maximal respiratory depth," however, was measured from multiple deep breaths on a recording spirometer.

Although there has been considerable speculation concerning changes in the residual volume and the total lung capacity, only a few actual measurements have been reported (36, 38). Anthony and Hansen (38), who determined the residual volume by the closed circuit hydrogen technique, found no change in the mean volume at term although again there was considerable individual variation. A slight decrease of the total lung capacity was attributed to a 30 per cent diminution of the expiratory reserve volume while the residual volume remained unchanged.

Ventilation and oxygen uptake have been studied much more extensively than lung volumes. A marked increase of the ventilatory requirement at rest was the most consistent finding (20, 29, 30, 33, 38, 40–44). The greater ventilation was usually the result of an augmented tidal volume. A review of previous work on oxygen uptake and metabolism is not within the scope of the present report. Briefly, oxygen consumption was usually

increased nearly as much as minute ventilation, and both resting ventilation and metabolism rose faster than body weight or surface area. Numerous reports concerning fetal metabolism and fetal body surface are available. When those factors were considered, the larger oxygen uptake appeared to be more nearly in line with calculated increases of metabolic requirement. Oxygen requirements did not increase excessively during exercise (33).

Dyspnea is a variable finding. It has been reported in 60 per cent of normal pregnant women (39). For some time it was assumed to be due to a decrease in vital capacity. More recently it has been suggested that dyspnea is related to the increased ventilatory requirement (32, 38).

The work of others suggested the importance of repeated examinations of the same patients. Previous contradictory findings may have been due to the fact that some subjects were examined relatively early during pregnancy and others at full term. Also, postpartum control values were obtained at periods varying from three days to nine months after delivery. Since previously observed changes of pulmonary function were usually small, it was thought important to obtain multiple determinations. It was hoped that this would reduce variations due to the training factor and that changes due to inaccuracies of the techniques of measurement would be minimized. The frequent observations of dyspnea during pregnancy suggested determinations of maximum breathing capacity, of resting and exercise breathing reserve, and of intrapulmonary distributional factors heretofore not measured during pregnancy.

PLAN OF INVESTIGATION

Selection of Subjects

Nineteen women from the Prenatal Clinic of the Boston City Hospital and from the Evangeline Booth Home volunteered for study. All but 2 were pregnant for the first time. All had normal chest roentgenograms. One woman with a history of minimal pulmonary tuberculosis was included. The disease was inactive, the lungs were normal on clinical and roentgenographic examinations, and initial pulmonary function was normal. In connection with another study (45), 4 patients were studied who had a history of rheumatic fever and showed clinical evidence of mitral stenosis. Only one of them remained asymptomatic throughout pregnancy and was classified as having class I heart disease (45). Pulmonary function was normal and it was thought proper to include her in this series. The other 17 patients were free of recognizable cardiorespiratory disease, and all of the 19 felt physically well.

Timing of Observations

An attempt was made to study all patients early during pregnancy. Most were first seen during the third month, but a few had initial studies in the fourth or fifth month. After the first visit, examinations were made at monthly intervals. With few exceptions the patients were seen during the week before confinement. Further observations were made before discharge from the hospital, usually

within six to ten days after delivery. It soon became apparent that the subjects could not cooperate fully so soon after delivery. Ventilatory efforts were hindered by pain and by a variety of bandages and binders. Examinations were therefore repeated, whenever possible, at least two months and preferably six months after delivery. Four women failed to return for later follow-up studies.

METHODS

Resting respiratory measurements were made early in the morning on non-fasting patients by closed-circuit oxygen-rebreathing spirometry. The tidal volume and minute ventilation were corrected to body temperature, ambient pressure, and saturated with water vapor (BTPS). The oxygen uptake was reduced to standard condition and dry (STPD). The ventilatory equivalent for oxygen was defined as the volume of air breathed per 100 cc. of oxygen absorbed but, as is customary, both volumes were expressed at BTPS for this calculation.

The maximum breathing capacity was collected with a high-velocity respiratory valve and Douglas bag for thirty seconds (46). The volume was measured in a Tissot spirometer, corrected to BTPS, and reported in liters per minute. The best of three efforts was recorded after consecutive efforts checked within 5 per cent. The predicted normal maximum breathing capacity was calculated according to sex, age, and body surface area (47). The vital capacity was measured in the upright and in the supine positions. Upright, the volume was collected in a spirometer equipped with a timing device for recording the total vital capacity as well as the timed capacities—the volumes exhaled during the first, the first two, and the first three seconds of the maximal expiratory effort (48). At least 70, 90, and 95 per cent of the total volume is normally exhaled during the three respective time intervals. The predicted vital capacity was calculated according to sex, age, and height (47). The air velocity index was calculated from the ratio: per cent of predicted maximum breathing capacity/per cent of predicted vital capacity. Values smaller than 0.8 were considered indicative of obstructive ventilatory insufficiency (49). The breathing reserve at rest was calculated as suggested by Baldwin and associates (48).

Exercise ventilation was measured with a high-velocity valve and a bag during the second, third, and fourth minutes of a level walk at the rate of 180 feet per minute (50); corrected to BTPS; and reported in liters per minute. The walking dyspnea index (reciprocal of "breathing reserve") was calculated by the ratio: 100 × walking ventilation/maximum breathing capacity (50).

The nomenclature for the components of the lung volume, proposed by the Pappenheimer Committee, was used throughout (51). The vital capacity and its subdivisions, the inspiratory capacity and the expiratory reserve, were recorded with a closed spirometer fitted with low resistance "J" valves and a rapidly moving kymograph drum. The volumes were corrected to BTPS, and the best of several efforts was recorded. The functional residual capacity was determined by an open-circuit oxygen-breathing technique (52), modified to minimize dead space correction, to eliminate "switching errors," and to assure adequate sampling of "alveolar" air (53). Early during the investigation a single determination of the functional residual capacity was made. It soon became evident that the volume changes were very small as pregnancy progressed. Therefore, to minimize errors in the technique, duplicate determinations were made on subsequent occasions. These were required to check within 5 per cent or 100 cc., whichever was less, and mean values were recorded. The residual volume was calculated by subtraction of the expiratory reserve from the functional residual capacity, and the total lung capcaity was obtained by addition of residual volume to vital capacity. The percentage of the total lung capacity occupied by the residual volume was expressed by the R.V./T.L.C. ratio.

The percentage of nitrogen remaining in the "alveolar air" after seven minutes of pure oxygen breathing is referred to as the intrapulmonary mixing index (52). This is never more than 1.5 per cent in normal subjects (53) according to the experience in this laboratory.

In addition to ventilatory studies, history and physical examination of heart and lungs were obtained initially on every patient. Roentgenograms were taken in full inspiration and on deep expiration. In many instances these roentgenographic studies were repeated at monthly intervals. Fluoroscopic observations were made to ascertain the extent of thoracic and diaphragmatic motion. Patients were questioned concerning dyspnea at the time of each examination, and a form designed to describe fully the type of dyspnea present was filled out by each patient after the study was completed.

RESULTS

The over-all changes in pulmonary function from the non-pregnant state to full term were analyzed for all 19 subjects. To define the non-pregnant state, the function studies obtained six months after delivery were chosen rather than the measurements made during the first trimester since it has been suggested that certain alterations in the respiratory pattern may occur very early in pregnancy (29, 33, 40, 41, 44). These values are tabulated under the heading "Not Pr." in tables 1 to 4 and they will be referred to subsequently as "control values." For the 4 patients on whom late follow-up studies could not be obtained, the data from the third month of pregnancy were used as control values since the results one to two weeks post partum were generally not comparable to late follow-up studies. All patients were seen during the last month of pregnancy, and results obtained at this time were tabulated under the heading "Term" in tables 1 to 4.

Vital statistics: The subjects' ages ranged from fifteen to thirty-seven years, but most were very young and the mean age was only twenty-two years (table 1). They gained an average of 10 kg., but individual gains varied from 1 to 17 kg. The body surface, read from the height-weight nomogram (54), increased 0.12 m^2 (figure 1). Because of the recurrent arguments in the literature concerning the calculation of the body surface during pregnancy, resting respiratory data were recorded as actual volumes rather than in the customary form of volume per square meter of body surface.

Resting respiratory data: The control values for resting respiratory data are shown in table 1 under the heading "Not Pr." A somewhat greater than basal oxygen uptake was expected since the patients had eaten breakfast, but this value was actually not elevated. Assuming 4.825 calories per liter of oxygen uptake (55) and a normal basal requirement of 37 calories per hour (56), the average "BMR" in the non-pregnant subjects was minus 4, or 35.5 calories per hour. The ventilatory requirement for this oxygen uptake appeared to be somewhat increased since the mean ventilatory equivalent was 3.0. Normally, approximately 2.5 liters of ventilation are required for an oxygen uptake of 100 cc. (57). Hyperventilation in normal subjects, commonly observed during closed spirometry, may be due to resistance breathing, a slightly elevated carbon dioxide tension of the inspired gas, and consciousness of the breathing effort. Four of the control values were obtained during the first trimester of pregnancy instead of six months after delivery. Since ventilation has been shown to increase very early during pregnancy (29, 33, 40, 44), inclusion of these data may have raised the average for the group.

TABLE 1—Vital Statistics and Resting Respiratory Data of 19 Normal Women, Not Pregnant and at Term

Patient Number	Age	Weight in Kilograms		Body Surface m^2		Resting									
						Tidal Volume cc., BTPS		Respiratory Rate		Minute Ventilation Liters, BTPS		Minute Oxygen Uptake cc., STPD		Ventilatory Equivalent for Oxygen L./100 cc.	
		Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term
1	22	58	70	1.63	1.77	500	685	14	14	7.00	9.59	199	241	2.9	3.3
2	25	77	82	1.79	1.90	560	1,340	14	11	7.84	14.74	215	231	3.0	5.3
3	24	59	72	1.61	1.75	395	625	14	15	5.53	9.38	204	255	2.2	3.1
4	23	58	70	1.68	1.82	455	540	15	17	6.83	9.18	204	255	2.7	3.0
5	27	82	88	1.92	1.98	430	625	14	15	6.02	9.38	213	244	2.3	3.1
6	21	54	63	1.57	1.68	410	635	17	15	6.97	9.53	181	233	3.2	3.4
7	19	78	84	1.93	2.00	610	820	13	15	7.93	12.30	258	292	2.6	3.5
8	25	48	61	1.43	1.58	330	555	23	21	7.59	11.66	191	255	3.3	3.8
9	21	54	66	1.64	1.78	405	520	20	20	8.10	10.40	182	404	3.7	2.1
10*	17	49	61	1.57	1.73	580	600	12	18	6.96	10.80	200	246	2.9	3.6
11	37	78	89	1.80	1.97	605	610	14	17	8.47	10.37	215	410	3.2	2.1
12†	22	46	61	1.45	1.63	485	580	14	16	6.79	9.28	205	230	2.7	3.3
13	20	60	70	1.69	1.79	425	490	24	22	10.20	10.78	214	236	4.0	3.8
14	20	48	65	1.44	1.73	585	785	16	14	9.36	10.99	210	294	3.7	3.1
15	15	53	58	1.56	1.62	450	645	11	12	4.95	7.74	189	215	2.2	3.0
16	18	64	73	1.68	1.77	485	625	17	17	8.25	10.63	195	285	3.5	3.1
17	18	49	64	1.58	1.72	525	780	13	14	6.83	10.92	181	246	3.1	3.6
18	21	50	58	1.50	1.60	420	605	14	16	5.88	9.68	180	195	2.7	4.1
19	20	56	57	1.61	1.64	605	820	11	11	6.66	9.02	190	285	2.9	2.6
Mean	22	59	69	1.64	1.76	487	678	15	16	7.27	10.34	201	266	3.0	3.3
Per cent difference		+17%		+7%		+39%		+10%		+42%		+32%		+10%	
Mean difference		+10 kg.		+0.12 m^2		+191 cc.		+1		+3.07 L.		+65 cc.		+0.3	
Standard deviation about the mean		±4.1 kg.		±0.06 m^2		±160 cc.		±2.2		±1.35 L.		±47 cc.		+1.0	
Standard error of the mean		±0.9 kg.		±0.013 m^2		±37 cc.		±0.5		±0.31 L.		±11 cc.		±0.3	
Mean/standard error (t)		10.6		9.2		5.2		2.0		9.9		5.9		1.6	
Probability of t		1%		1%		1%		10%		1%		1%		20%	

* Mitral stenosis, asymptomatic. † Minimal tuberculosis, inactive.

Resting respiratory data at term showed more consistent changes than any other measures of pulmonary function (table 1). Although there was some individual variation as to magnitude, there was, with the exception of the respiratory rate, no variation of the direction of these changes. The oxygen uptake for the group increased from 201 to 266 cc., or 32 per cent. The hourly caloric requirement at term was 43.8, with a change of "BMR" from minus 4 to plus 18. However, the latter value has little meaning because the fetal body surface and metabolism were not considered in the calculation. The 42 per cent increment of minute ventilation at term was the largest change of any of the measured functional values. It was considerably greater than the increments of body surface or body weight (figure 1). Because the ventilation also rose somewhat

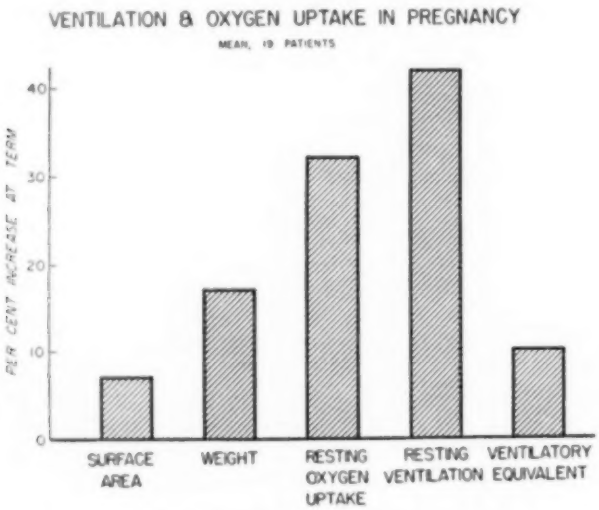

FIG. 1. Per cent increase of body surface area, weight, resting oxygen uptake, ventilation, and ventilatory equivalent during the course of pregnancy. Mean values for 19 normal women.

faster than oxygen uptake, the ventilatory equivalent for oxygen increased from 3.0 to 3.3 liters per 100 cc. at term (table 1, figure 1). A larger tidal volume was chiefly responsible for the greater ventilation. The mean respiratory rate increased only one breath per minute, and individual variation of the change in rate was so great that no significant trend could be discerned.

Dynamic exchange of air: The average maximum breathing capacity was 102 liters per minute, or 102 per cent of predicted, while the patients were not pregnant; and 96 liters per minute, or 91 per cent, at term (table 2). Changes in individual subjects varied, and 5 showed a reversal of this trend. The altered weight without change in stature during pregnancy caused difficulty in calculating a dependable normal predicted maximum breathing capacity. As preg-

TABLE 2—Maximal Breathing, Total and Timed Capacities During Pregnancy

Patient Number	Maximum Breathing Capacity				Air Velocity Index		Upright Vital Capacity									
	L./Min.		Per Cent of Predicted				Liters		Per Cent of Predicted		Per Cent in First Second		Per Cent in First 2 Seconds		Per Cent in First 3 Seconds	
	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term
1	112	101	113	101	1.11	0.99	3.31	3.31	102	102	84	72	87	91	97	95
2	124	143	116	120	1.02	1.07	3.91	3.88	114	112	80	83	92	91	95	94
3	113	99	105	89	1.14	1.07	2.98	2.68	92	83	—	—	—	—	—	—
4	118	101	116	96	1.02	0.88	3.77	3.60	114	109	74	73	86	88	92	91
5	109	115	97	104	0.84	0.90	3.73	3.73	116	116	—	—	—	—	—	—
6	92	100	95	97	1.06	1.05	2.90	2.95	90	92	85	82	96	90	100	94
7	96	99	80	79	0.69	0.77	4.00	3.49	116	102	86	81	93	92	97	96
8	80	72	90	76	1.06	0.85	2.52	2.65	85	89	89	87	100	96	100	100
9	109	90	108	83	1.08	0.86	3.38	3.33	100	97	83	85	94	97	100	100
10*	106	91	108	90	1.33	1.26	2.80	2.71	81	72	84	83	94	93	99	95
11	81	75	84	75	0.92	0.85	2.59	2.52	91	88	75	77	85	90	93	95
12†	98	96	108	97	1.14	0.96	3.00	3.18	95	101	90	91	100	100	100	100
13	84	72	80	65	0.88	0.71	3.01	3.01	91	91	78	79	94	94	98	100
14	71	74	80	79	0.79	0.83	3.10	2.91	101	95	80	82	96	96	100	100
15	119	113	119	110	1.16	1.12	3.40	3.23	103	98	85	83	100	95	100	99
16	103	89	97	80	1.05	0.86	2.94	2.99	92	93	94	88	96	96	96	97
17	82	66	85	61	0.96	0.67	2.99	3.05	89	91	90	94	100	100	100	100
18	95	93	104	95	1.16	1.06	2.82	2.82	90	90	76	77	88	97	93	100
19	155	131	155	128	1.38	1.16	3.65	3.60	112	110	96	86	97	97	99	99
Mean	102	96	102	91	1.04	0.94	3.20	3.14	99	96	84	82	94	94	98	97
Per cent difference	−6%		−11%		−10%		−2%		−3%		—		—		—	
Mean difference	−6 L.		—		—		−0.06 L.		—		—		—		—	
Standard deviation about the mean	±11 L.		—		—		±0.16 L.		—		—		—		—	
Standard error of the mean	±2.5 L.		—		—		±0.04 L.		—		—		—		—	
Mean/standard error (t)	2.4		—		—		1.5		—		—		—		—	
Probability of t	5%		—		—		20%		—		—		—		—	

* Mitral stenosis, asymptomatic. † Minimal tuberculosis, inactive.

nancy progresses, the predicted values increase according to the regression equation (47). Although the per cent of predicted values are recorded, it will be preferable to focus attention on actual performance (table 2).

TABLE 3

BREATHING RESERVE AT REST AND DURING EXERCISE, AND INTRAPULMONARY MIXING INDEX DURING PREGNANCY

PATIENT NUMBER	BREATHING RESERVE, PER CENT		WALKING VENTILATION, L./MIN. (BTPS)		WALKING DYSPNEA INDEX, PER CENT		INTRAPULMONARY MIXING INDEX, PER CENT ALVEOLAR N_2	
	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term
1	94	90	14.5	18.1	13	18	0.27	0.43
2	94	90	16.0	24.2	13	17	0.35	0.27
3	95	91	17.3	19.3	16	10	1.06	0.81
4	92	91	21.0	29.4	18	29	0.72	0.29
5	95	92	19.0	25.1	18	22	0.64	0.66
6	93	90	11.8	17.0	13	17	0.50	0.33
7	89	88	14.5	19.5	15	20	0.70	0.25
8	90	85	14.7	19.0	18	26	0.70	0.36
9	95	89	15.8	15.2	15	17	0.72	0.60
10*	93	88	13.9	20.4	13	23	0.42	0.55
11	90	87	19.2	22.0	24	29	0.62	0.35
12†	92	91	10.5	13.5	13	14	0.34	0.24
13	87	85	15.8	18.9	19	26	0.85	0.58
14	87	86	13.6	16.2	19	22	0.39	0.59
15	96	94	8.8	12.7	7	11	0.33	0.58
16	92	88	15.0	22.6	15	25	0.59	0.40
17	90	83	12.7	17.6	15	27	0.41	0.89
18	94	89	13.5	18.0	15	19	0.68	0.35
19	95	93	11.0	15.1	7	12	0.64	0.29
Mean	92	89	14.7	19.1	15	21	0.56	0.46
Per cent difference	−3%		+30%		+40%		—	
Mean difference	—		+4.4 L.		—		—	
Standard deviation about the mean	—		±2.2 L.		—		—	
Standard error of the mean	—		±0.5 L.		—		—	
Mean/standard error (t)	—		8.8		—		—	
Probability of t	—		1%		—		—	

* Mitral stenosis, asymptomatic.

† Minimal tuberculosis, inactive.

The average air velocity index of 1.04 during the control period was within normal limits; the decrease of the mean to 0.94 was due to both a smaller actual maximum breathing capacity and a larger predicted value. The loss of vital capacity in the upright position from 3.20 to 3.14 liters at term amounted to 2 per cent. No significant trend could be observed; approximately half of the patients showed a slight increase, while the others showed a small decrease. The

timed vital capacities showed that 84 per cent of the total volume was exhaled in the first second, 94 per cent during the first two seconds, and 98 per cent in the first three seconds. All individual performances were well within normal limits (table 2). There was no significant change in these figures at term.

Breathing reserve at rest and during exercise: In 3 of the subjects, the breathing reserve was below 90 per cent during the control period, and at term 10 patients showed values which were below this lower limit of normal (table 3).

The normal ventilatory requirement during the standard walking exercise used in this laboratory has been found to be 10 liters plus or minus 1 liter per minute

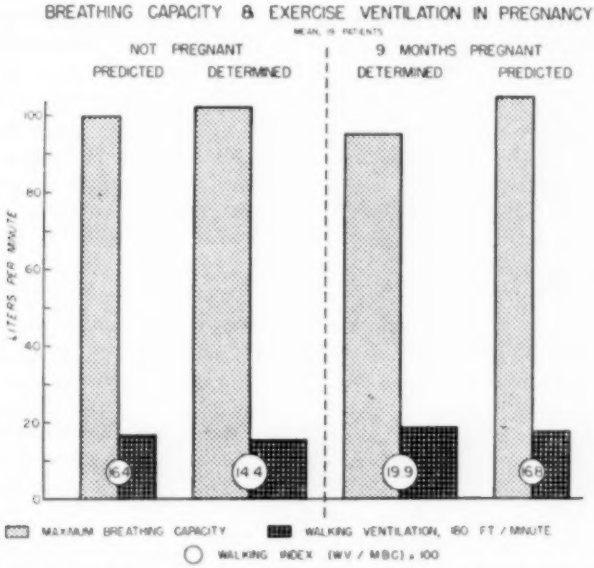

FIG. 2. Mean values of maximum breathing capacity, walking ventilation, and walking dyspnea index for 19 normal women when not pregnant and during the ninth month of pregnancy. Predicted normal values for the group are calculated from the body surface area. Consequently, as pregnancy advances, these values increase.

per square meter of body surface. The mean walking ventilation of the subjects was 14.7 liters (9 L. per minute per m^2B.S.) during the control period and increased to 19.1 liters (11 L. per minute per m^2B.S.) at term (table 3, figure 2). The hyperventilation, which was so consistently exhibited at rest, was not observed during exercise, and the ventilatory requirement during exercise increased less than resting ventilation as pregnancy progressed. The walking dyspnea index, the percentage of the maximum breathing capacity required for this exercise, increased 40 per cent (figure 2). At term this index remained below 20 per cent in nearly one-half of the subjects; and 35 per cent, the point where clinical dyspnea is usually expected, was never reached.

Distributional factors: The intrapulmonary mixing index is not a very sensitive measurement of distributional defects but some significance may be attached to readings above 1.5 per cent (53). The mean indices of 0.56 per cent before, and 0.46 per cent during, pregnancy (table 3) were lower than values obtained in this laboratory in normal volunteers. It was thought that the moderate hyperventilation at rest was responsible for the more perfect flushing of the lungs. Similar low indices are encountered after pneumonectomy when the remaining lung has to ventilate twice the usual amount to provide for adequate respiratory exchange at rest (58). The final nitrogen recovered was probably derived solely from nitrogen excreted by the body tissues during the test.

Lung volumes: During the control period, the vital capacity in the supine position (table 4) was almost identical with the same volume determined in the upright position (table 2) and was equal to the predicted volume calculated from the regression equation. The 1 per cent increase at term was too small to signify a trend. Of more significance and greater magnitude were the changes in the subdivisions of the vital capacity. The mean inspiratory capacity increased 120 cc., or 5 per cent, and, in individual subjects, the changes were moderately consistent. Six patients failed to show the characteristic trend. Changes of the expiratory reserve in the opposite direction were even more uniform. The 100 cc. average diminution represented a loss of 15 per cent (table 4).

The decrease of the residual volume from 965 to 770 cc. was greater than the loss of expiratory reserve. This change was seen in all but one patient (table 4). The total lung capacity diminished 4 per cent at term since the smaller residual volume and expiratory reserve were not quite offset by an increase of the inspiratory capacity (figure 3). The mean residual volume occupied a normal 23 per cent of mean total lung capacity during the control period and 19 per cent at term. At term, the residual volume was as little as 16 per cent of the total capacity in 5 patients. Such low values are rare in normal individuals but are common in patients with pneumoperitoneum (23) and with extrapleural pneumothorax (59). The low residual volume explains the nearly atelectatic appearance of the lung fields on roentgenograms taken during fullest expiration near the end of pregnancy.

Of greatest importance, from the standpoint of collapse therapy, is the volume occupied by the lung at the end of normal expiration, the functional residual capacity. This decreased 295 cc., or 18 per cent, during the course of pregnancy (figure 3). The change of the functional residual capacity could be singled out from all other observations by one fact; it was the only measurable change which occurred without exception in every individual subject.

The percentage of the total lung capacity occupied by the functional residual capacity, although not usually calculated (36), is a better index of pulmonary function during collapse therapy than the R.V./T.L.C. ratio. Since the normal residual volume in young subjects amounts to 20 per cent of the total lung capacity and the expiratory reserve is normally 20 per cent of the vital capacity, the "predicted" functional residual capacity is 36 to 40 per cent of the entire lung volume. In the experimental subjects, this ratio was 38 per cent during the

TABLE 4—Lung Volumes During Pregnancy

Patient Number	Inspiratory Capacity, cc.		Expiratory Reserve, cc.		Vital Capacity, cc.		Functional Residual Capacity, cc.		Residual Volume, cc.		Total Lung Capacity, cc.		R.V. × 100, T.L.C. Per Cent	
	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term	Not Pr.	Term
1	2,660	2,950	665	515	3,325	3,465	1,445	1,195	780	680	4,105	4,145	19	16
2	3,180	3,410	610	470	3,790	3,880	1,560	1,240	950	770	4,740	4,650	20	16
3	2,550	2,390	555	490	3,105	2,880	1,300	1,040	745	550	3,850	3,430	19	16
4	2,935	3,370	830	625	3,765	3,995	2,000	1,420	1,170	795	4,935	4,790	24	16
5	2,720	3,005	910	800	3,630	3,805	1,820	1,595	910	795	4,540	4,600	20	17
6	2,310	2,405	565	645	2,875	3,050	1,520	1,445	955	800	3,830	3,850	25	21
7	3,170	3,500	405	450	3,575	3,950	1,350	1,215	945	765	4,520	4,715	21	16
8	1,980	2,480	495	340	2,475	2,820	1,385	1,190	890	850	3,365	3,670	26	23
9	2,670	2,650	955	770	3,625	3,420	1,830	1,465	875	695	4,500	4,115	19	17
10*	2,410	2,510	520	455	2,930	2,965	1,305	1,115	785	660	3,715	3,625	21	18
11	2,340	2,315	415	435	2,755	2,815	1,540	1,275	1,125	840	3,880	3,655	29	23
12†	2,835	3,070	620	500	3,455	3,570	1,610	1,355	990	855	4,445	4,425	22	19
13	2,495	2,180	450	475	2,945	2,655	1,470	1,360	1,020	885	3,965	3,540	26	25
14	2,680	2,380	740	685	3,420	3,065	1,730	1,650	990	965	4,410	4,030	22	24
15	2,925	3,040	900	710	3,825	3,750	1,675	1,515	775	805	4,600	4,555	17	18
16	2,515	2,305	425	225	2,940	2,850	1,405	795	980	570	3,920	3,420	25	17
17	2,295	2,380	660	545	2,955	2,925	1,800	1,310	1,140	765	4,095	3,690	28	21
18	2,250	2,630	800	570	3,050	3,200	1,860	1,450	1,060	880	4,110	4,080	26	22
19	2,970	3,170	930	790	3,900	3,960	2,160	1,590	1,230	800	5,130	4,760	24	17
Mean	2,625	2,745	655	555	3,280	3,300	1,620	1,325	965	770	4,245	4,070	23	19
Per cent difference	+5%		−15%		+1%		−18%		−20%		−4%		−17%	
Mean difference	+120 cc.		−100 cc.		+20 cc.		−295 cc.		−195 cc.		−175 cc.		−4%	
Standard deviation about the mean	±221 cc.		±97 cc.		±227 cc.		±148 cc.		±124 cc.		±278 cc.		—	
Standard error of the mean	±51 cc.		±22 cc.		±52 cc.		±34 cc.		±28 cc.		±64 cc.		—	
Mean/standard error (t)	2.3		4.5		0.4		8.7		7.0		2.7		—	
Probability of t	5%		1%		70%		1%		1%		2%		—	

* Mitral stenosis, asymptomatic. † Minimal tuberculosis, inactive.

control period and only 32 per cent at term. The volume to which the lungs are distended during quiet breathing at term is therefore considerably smaller than in normal non-pregnant individuals.

Results of serial examinations during and after pregnancy: Repeated studies during the course of pregnancy appeared important. Often, changes reported by other investigators at term were so small that a training factor alone could have been responsible for them.

The role of training has been evaluated in the past by comparing observations during pregnancy with observations of non-pregnant women of a similar age distribution studied

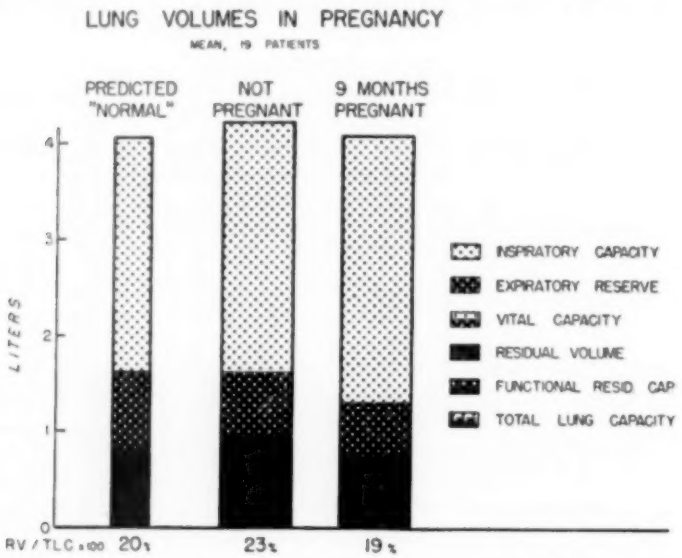

FIG. 3. The average total lung capacity and its subdivisions of 19 normal subjects when not pregnant and during the ninth month of pregnancy. Predicted normal values for the group are shown.

at the same time intervals. This protocol suggested that improvement of the vital capacity during pregnancy was not due to training (32). It seemed preferable to eliminate changes due to training by providing thorough experience with the various tests by multiple trials on the same occasion and by serial examinations repeated at short intervals. This seemed particularly important for the maximum breathing capacity where training has been shown to play a definite role during the first few trials (60).

In certain other tests not requiring the subject's cooperation, the technical determinations are difficult and repeated studies are necessary to cancel out mechanical inaccuracies. Multiple studies also tend to reduce the variability of physiologic conditions. This applies particularly to the study of respiration and metabolism at rest and to the determination of the functional residual capacity.

Finally, examinations at regular intervals seemed important because observations

made only at term and after delivery might not reveal maximal changes encountered during pregnancy. Circulatory studies have shown that the increases of blood volume and cardiac output are greatest during the sixth month (33). The peak of ventilatory and respiratory changes might also occur at a time other than full term. Indeed, a nonlinear progression of changes has been demonstrated for the vital capacity (32, 33). Dyspnea is often less severe or absent at the end of pregnancy, suggesting that sudden alterations in ventilatory function might accompany the descent of the fetus into the pelvic inlet. Hence, a special effort was made to study function during the last week before delivery.

Mean values of observation of 9 patients seen at monthly intervals during pregnancy, one to two weeks after delivery, and six months later are shown in tables 5 and 6 and in figures 4 and 5.

In table 5 the resting and exercise data are shown as total volumes and as volumes per square meter of body surface. In table 6 the upright vital and maximum breathing capacities are recorded both as observed and as per cent of predicted values. The total lung capacities and their subdivisions are indicated as per cent of the predicted normal volumes for the group. In figures 4 and 5 the per cent changes with time are plotted on the assumption that the observations six months after delivery represented normal performance both for the period before, and the period some time after, pregnancy. The progressive alterations of pulmonary function will be discussed in the light of this assumption.

First Trimester

The only definite changes observed during the third month of pregnancy were the marked elevation of tidal volume and minute ventilation. The ventilatory equivalent was larger than during the control period since oxygen uptake was only slightly increased. The ventilatory requirement during exercise was normal and the maximum breathing capacity and all subdivisions of the total lung capacity varied by no more than plus or minus 4 per cent from the control values obtained six months after delivery. This good agreement suggests that any improvement due to training was confined to the first few efforts during the first examination.

Second Trimester

During the second trimester of pregnancy, a gradual increase of ventilation at rest was accompanied by a nearly parallel rise of oxygen uptake, and the initially large ventilatory equivalent remained unaltered. The remaining observations were unchanged during the early part of the second trimester. During the sixth month, marked enlargement of the uterus was accompanied by significant increase of body weight and surface area and a corresponding rise of exercise ventilatory requirement, while the typical changes in the subdivisions of the total lung capacity made their first appearance. The expiratory reserve and the residual volume began to decrease while the inspiratory capacity increased. The maximum breathing capacity, vital capacity, and total lung capacity were not affected.

TABLE 5

SERIAL OBSERVATIONS OF RESTING AND EXERCISE VENTILATION DURING AND AFTER PREGNANCY

Mean Values for 9 Patients*

TIME OF OBSERVATION	BODY SURFACE, m^2	TIDAL VOLUME, CC.	RESPIRATORY RATE	MINUTE VENTILATION		MINUTE OXYGEN UPTAKE		VENTILATORY EQUIVALENT L./100 CC.	BREATHING RESERVE, PER CENT	MINUTE VENTILATION		WALKING DYSPNEA INDEX, PER CENT
				Liters	L./m^2B.S.	cc.	cc./m^2B.S			L.	L./m^2B.S.	
3 months' pregnant	1.62	565	16	8.70	5.37	217	134	3.3	91	14.5	9.0	15
4 months' pregnant†	1.63	595	15	9.13	5.60	219	134	3.5	91	14.9	9.1	15
5 months' pregnant	1.65	615	16	10.00	6.06	226	137	3.6	90	15.2	9.2	16
6 months' pregnant	1.67	615	16	9.73	5.82	228	137	3.5	90	16.2	9.7	17
7 months' pregnant	1.70	655	16	10.33	6.07	234	138	3.6	90	17.1	10.1	18
8 months' pregnant	1.72	700	16	11.02	6.40	243	141	3.7	89	19.7	11.5	20
9 months' pregnant	1.73	695	16	11.02	6.36	238	138	3.8	89	20.3	11.7	21
1 to 2 weeks post partum	1.65	550	17	9.48	5.74	229	139	3.4	90	18.1	11.0	20
4 to 9 months post partum	1.63	470	16	7.43	4.55	196	120	3.1	92	15.0	9.2	15

* Patients Nos. 1, 2, 3, 4, 5, 7, 12, 13, and 14 of tables 1 through 4.

† One of the 9 patients was not seen at this time. For this patient, the average of observations at the third and fifth months were used.

TABLE 6

SERIAL OBSERVATIONS OF MAXIMAL VENTILATION, LUNG VOLUMES, AND INTRAPULMONARY MIXING DURING AND AFTER PREGNANCY
Mean Values for 9 Patients*

TIME OF OBSERVATION	MAXIMUM BREATHING CAPACITY		UPRIGHT VITAL CAPACITY		AIR VELOCITY INDEX	INSPIRATORY CAPACITY PER CENT PREDICTED	EXPIRATORY CAPACITY PER CENT PREDICTED	VITAL CAPACITY PER CENT PREDICTED	FUNCTIONAL RESIDUAL CAPACITY PER CENT PREDICTED	RESIDUAL VOLUME PER CENT PREDICTED	R.V. T.L.C. X 100, PER CENT	MIXING INDEX, PER CENT N_2
	L./Min.	Per Cent Predicted	L.	Per Cent Predicted								
3 months' pregnant	97	99	3.20	100	0.99	107	86	102	102	118	23	0.65
4 months' pregnant†	99	100	3.21	100	1.00	108	86	103	101	116	22	0.53
5 months' pregnant	97	97	3.19	100	0.97	108	85	102	101	116	22	0.55
6 months' pregnant	96	95	3.23	101	0.94	109	80	102	96	112	22	0.55
7 months' pregnant	97	94	3.21	100	0.94	116	83	108	95	106	20	0.54
8 months' pregnant	97	93	3.31	103	0.90	115	74	105	87	99	19	0.41
9 months' pregnant	97	92	3.26	102	0.90	115	71	104	85	98	19	0.38
1 to 2 weeks post partum	92	92	3.10	97	0.95	105	73	97	95	116	23	0.58
4 to 9 months post partum	102	102	3.31	103	0.99	111	86	104	101	117	22	0.53

* Patients Nos. 1, 2, 3, 4, 5, 7, 12, 13, and 14 of tables 1 through 4.

† One of the 9 patients was not seen at this time. For this patient the average of observations made at the third and fifth months were used.

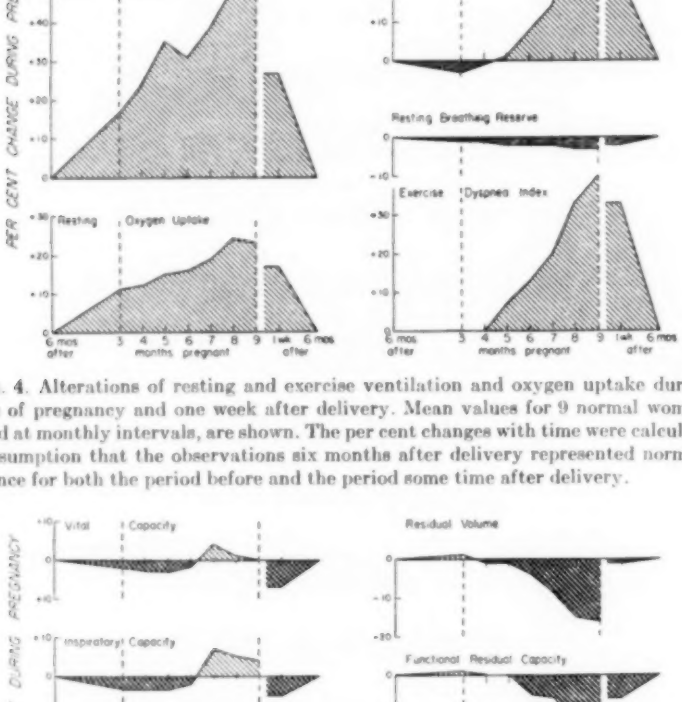

FIG. 4. Alterations of resting and exercise ventilation and oxygen uptake during the course of pregnancy and one week after delivery. Mean values for 9 normal women, examined at monthly intervals, are shown. The per cent changes with time were calculated on the assumption that the observations six months after delivery represented normal performance for both the period before and the period some time after delivery.

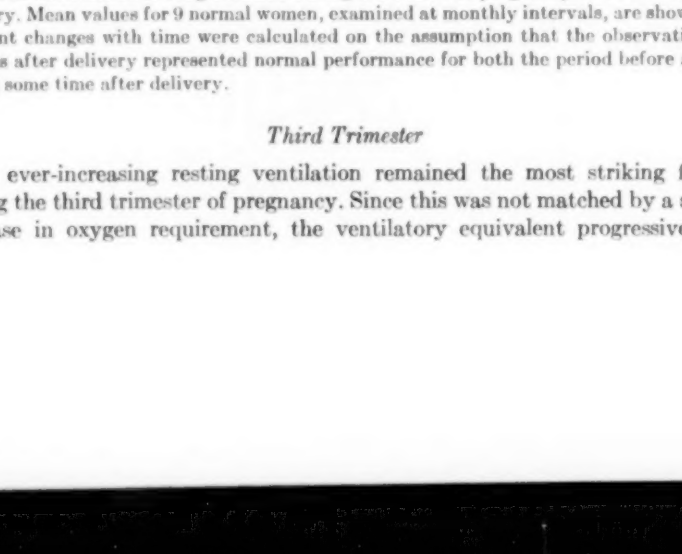

FIG. 5. Alterations of lung volumes during the course of pregnancy and one week after delivery. Mean values for 9 normal women, examined at monthly intervals, are shown. The per cent changes with time were calculated on the assumption that the observations six months after delivery represented normal performance for both the period before and the period some time after delivery.

Third Trimester

An ever-increasing resting ventilation remained the most striking finding during the third trimester of pregnancy. Since this was not matched by a similar increase in oxygen requirement, the ventilatory equivalent progressively in-

creased up to the ninth month. In spite of an unaltered maximum breathing capacity, the breathing reserve at rest decreased below 90 per cent. The exercise ventilation for the first time outdistanced the rise in body surface area. Because of the appearance of hyperventilation during exercise, the walking ventilation, corrected for surface area, was elevated and the walking dyspnea index rose above 20 per cent. The functional residual capacity and its components, the expiratory reserve, and residual volume continued to diminish and the residual volume occupied less than 20 per cent of the total lung capacity only during this period. During the seventh and eighth months this loss of volume was matched by a progressive increase of the inspiratory capacity, but at term the decrease of functional residual capacity was far greater than the increase of inspiratory capacity, and the total lung capacity was slightly reduced. Early during this period the vital capacity was slightly larger than during the control period in both the supine and the upright positions. Although this increment was never more than 5 per cent, this observation may confirm those of previous investigators who described a peak of vital capacity during the seventh and eighth months (33). The studies obtained shortly before delivery (nine months) did not explain the relief from dyspnea frequently experienced at this time. The changes in the various subdivisions of the lung volume were maintained, suggesting that the descent of the uterus into the pelvis was not accompanied by a marked diminution of the intra-abdominal pressure.

Early Postpartum Period

Observations one to two weeks after delivery showed that this was a definitely abnormal period. Many of the subjects felt tired, some had pain and were "not quite up to it." A number of women correctly predicted that they would not perform as well as on previous occasions. Others felt encumbered by breast binders and abdominal or perineal supports which could not be removed at this time.

Resting ventilation and oxygen uptake remained high although not at the peak reached at term. Others have commented on the continued elevation of the basal metabolic rate for some days after delivery (29, 44, 61). Slight anemia, a low-grade fever, and the excitement of leaving the hospital may have been among the factors involved. The same influences may have been responsible for a persisting elevation of exercise ventilation. Voluntary maximal performance was poor. The maximum breathing capacity was significantly decreased only during this period, and this was the only time when the vital and inspiratory capacities were decreased and the residual volume increased.

Experiences with these subjects during the first two weeks after delivery suggest that the results of others who obtained their control values during this period should be viewed with some reservation. If the early postpartum observations had been accepted as normal performance, it would have been erroneously concluded that resting and exercise ventilatory requirements are only slightly elevated during pregnancy and that the maximum breathing capacity and vital capacity are markedly increased at term.

Dyspnea During Pregnancy

Shortness of breath was evaluated in three ways:

(*1*) Specific questions were asked at each visit.

(*2*) Patients were observed at rest and during activity and questioned immediately after the standard exercise.

(*3*) After completion of all studies, the patients received a questionnaire dealing with numerous details of dyspnea before, during, and after pregnancy.

There was poor agreement among the three types of analyses of dyspnea. For example, some patients did not complain of dyspnea during the exercise test;

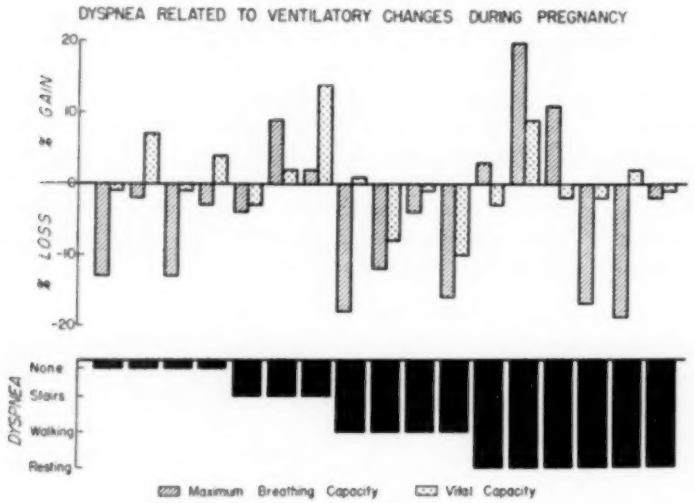

FIG. 6. Per cent changes of maximum breathing capacity and vital capacity during the course of pregnancy. Data of 17 normal women are arranged according to the degree of dyspnea noted during pregnancy by individual subjects.

yet, in retrospect, on the questionnaire they claimed considerable dyspnea at low levels of activity.

Thirteen patients, or 68 per cent, complained of dyspnea during pregnancy and corroborated their statements in the later questionnaire. Two patients were apparently unable to understand questions dealing with shortness of breath and they confused discomfort during breathing with palpitation, anxiety, fatigue, and the normal ventilatory response to exercise. The remaining 17 patients were arranged according to the degree of dyspnea they encountered during pregnancy. Alterations of maximum breathing capacity and upright vital capacity, expressed as per cent loss or gain, were compared to the subjective complaints (figure 6). There appeared to be no correlation. On the contrary, a few with a definite reduction of maximum breathing capacity were among those who failed

to complain of shortness of breath at any level of activity. Others with unchanged or improved ventilatory function complained of dyspnea at rest. Similar comparisons of dyspnea with alterations of resting ventilation, dyspnea index, breathing reserve, oxygen uptake, and subdivisions of the total lung capacity failed to show any significant correlation.

DISCUSSION

The presentation of results has centered on changes which were expressed as arithmetical means for the group. The percentage changes were also calculated to relate the difference to the initial values. In certain instances attention was called to the variability of individual responses.

In previous studies of the effect of disease or therapy on pulmonary function, individual differences have been clustered so closely around the mean that it could confidently be predicted that further measurements would not greatly alter the results. This was true for certain measurements in the present investigation. For example, further assessment of the statistical significance of the changes in resting ventilation seemed unnecessary. If more women had been tested, it is highly improbable that the difference between the mean ventilation during the control period and at term would eventually be reduced to zero. This was not true in the case of the vital capacity. Large positive and negative changes among individuals were common and the mean difference between the control studies and the results at term was small. It seemed likely that the observed small mean difference was due rather to random sampling than to a true trend. For some of the other results it appeared necessary to quantitate the significance of the observed change.

The following statistical expressions are indicated in tables 1 to 4.

> From the standard deviation (S.D.), the standard error (S.E.) was calculated as an index of the variability of the derived mean (62). The figure under the heading "t" in each column indicates how many times larger the mean was than its standard error. Since the number of individuals was relatively small, the probability of obtaining, by random sampling, t values as great as, or greater than, the specified value was assessed by referring to Fisher's table for t (63). The probability of t, recorded in the last horizontal column in tables 1 to 4, indicates in per cent what the chances are that the observed average changes were due to random sampling. Thus, the probability of t for the increase in minute ventilation (table 1) was much less than 1 per cent. In other words, the odds were greater than 1 to 100 against the chance of finding such a high value for t if the true mean change had been zero. In contrast, there was a 60 to 70 per cent likelihood that the change of the vital capacity (table 4) was due to chance sampling and not due to the altered conditions of pregnancy. In general, a change of the mean can be accepted as statistically significant if the probability of t is at the 5 per cent level or less.

As expected, the increases with pregnancy of body weight, surface area, tidal volume, minute ventilation, and oxygen uptake were highly significant (table 1). The smaller mean changes of respiratory rate and ventilatory equivalent were

within the limits of chance variation. The increment of exercise ventilation, while smaller percentage-wise than the increment of resting ventilation, was nevertheless equally important. The slight mean reduction of the vital capacity in the upright position and the equally small mean increase of this volume in the supine position were probably due to chance. The other shifts in the subdivisions of the lung volume were highly significant (table 4).

During the early part of pregnancy the only significant change in pulmonary function was increased ventilation at rest. Since this was not accompanied by a corresponding increase of oxygen uptake, it may be designated as true hyperventilation. It has been thought that the enlarging uterus impedes the movement of the diaphragm and hence reduces tidal excursions. Hyperventilation was explained by the resulting increased proportion of dead space to alveolar ventilation. The diaphragm, however, is not elevated during early pregnancy, and even during the last months it moves at least as well as in non-pregnant subjects (20, 21, 22, 64). Lung volume studies in the present investigation showed that neither tidal nor maximal excursions were impeded at any time during the course of pregnancy (tables 4, 6). The increased minute ventilation is affected by a larger tidal volume and is not accompanied by tachypnea. The dead space/alveolar ventilation ratio is therefore actually reduced rather than increased. Assuming a constant dead space of 140 cc., alveolar ventilation increased 68 per cent in the 9 patients, while total ventilation increased only 48 per cent at term (table 5). Actually, because of the reduced functional residual capacity, the dead space was probably smaller at term than during the control period, and the increment of alveolar ventilation was even larger.

Local factors may be responsible for hyperventilation. An increased ventilation requirement for a given oxygen uptake may be due to an augmented dead space, unsatisfactory intrapulmonary distribution of gases, defective diffusion across the aveolo-capillary membrane, or any combination of these factors. The physiologic dead space is not increased during pregnancy; on the contrary, the present observations would indicate that it is slightly reduced at rest. Intrapulmonary mixing studies failed to demonstrate impaired distribution. The diffusion coefficient for oxygen has not been estimated during pregnancy, and it is doubtful whether presently available methods could demonstrate a minimal defect if it existed. The only factors which could be responsible for altered diffusion are circulatory. The effect of increased blood volume has not been explored in this regard. At any rate, this factor could not be operative during the first trimester when circulatory changes have not yet occurred.

Altered afferent impulses from the lung cannot be considered in the mechanism of hyperventilation as long as the state of inflation of the lungs is not altered during quiet breathing. Even during the later months of pregnancy, when the volume of the lungs at rest is diminished, altered stretch reflexes have probably little effect on minute ventilation since no change was observed during treatment with artificial pneumoperitoneum (23).

Factors other than physical may be responsible for hyperpnea. The difficulties of measuring "basal" ventilation are great even if the apparatus offers little

resistance to breathing. However, comparison with ventilation before conception in the same patients has shown that hyperpnea early during pregnancy is not due to "voluntary" hyperventilation (33, 41, 29, 40). Ventilation during pregnancy has been measured with a pneumotachograph to minimize resistance breathing and subjective factors (65). Under these ideal circumstances, the increment of minute ventilation ranged from 20 to 240 per cent, and a definite change was observed as early as the first month of pregnancy. It is apparent that factors other than the physical enlargement of the uterus or local changes in the lungs must be responsible for the marked hyperpnea of pregnancy.

Pregnancy is accompanied by numerous nervous, hormonal, and biochemical changes which must be scrutinized as possible bases of hyperpnea. A reduction of the alkaline reserve, with lowered alveolar and arterial carbon dioxide tension, and a low blood plasma carbon dioxide content and combining power have been repeatedly demonstrated (67, 68). These changes can be shown as soon as the first menstrual period has been missed. A resulting increased concentration of hydrogen ions, ketosis or "acidosis of pregnancy," has been held responsible for hyperpnea (30, 69). More recently the reduced alkaline reserve has been thought to be due to a diminution of fixed base and a concomitant and equal reduction of anion content of the plasma (44, 68). This has led to the conclusion that hyperpnea is due to central stimuli and that the changes in the acid-base balance are secondary adjustments to the resulting carbon dioxide deficit (44). There is some evidence that hyperpnea during pregnancy is due to an altered threshold of the respiratory center (65). Acid-base changes, similar to those occurring during pregnancy, can be produced by prolonged induced hyperventilation and are also seen during hyperpnea of encephalitic origin. It is known that the intensity and duration of nervous stimuli required to produce muscular contraction are shortened during pregnancy. The early nausea and vomiting of pregnancy, central in origin, constitute further evidence of heightened nervous irritability.

Collapse, defined as a decreased volume of the lungs, and rest, defined as a reduced functional activity of the lungs, have been abundantly shown to have a beneficial effect on pulmonary tuberculosis. Late pregnancy causes a marked diminution of the functional residual capacity which is the end-expiratory volume of the lungs of inactive patients. In this regard the "collapse" due to pregnancy is as effective as artificial pneumoperitoneum (23) and as effective, if not as selective, as therapeutic intrapleural pneumothorax (70). Unlike intrapleural pneumothorax or thoracoplasty, pregnancy does not prevent normal maximal expansion of the lungs. However, the uninterrupted ability to fill the lungs to a normal lung capacity does not appear to detract from the effectiveness of certain collapse procedures, particularly pneumoperitoneum (23) and extrapleural pneumothorax (70). It appears that, in the absence of any other changes due to pregnancy, the diminution of the volume of the lungs in the pulmonary resting position should exert a favorable effect on the course of pulmonary tuberculosis during the second half of pregnancy.

In regard to functional activity, pregnancy has an effect opposite to that of unilateral collapse therapy. The basal oxygen requirement is increased and, for

a given oxygen uptake, a larger ventilatory effort is necessary. During the entire pregnancy the resting woman is at a considerable exercise level as far as ventilation is concerned, and during the later months of pregnancy any given activity requires more work for the lungs than in non-pregnant women. In the absence of any other changes during pregnancy, the additional work for the lungs should be expected to have an unfavorable effect on the course of pulmonary tuberculosis. This factor is probably minimized because physical activity is usually voluntarily limited during pregnancy.

A more detailed discussion of the interplay of pulmonary and other factors on the course of pulmonary tuberculosis during and immediately after pregnancy will be made in the second paper of this series (23).

The additional demands on the respiratory apparatus due to pregnancy are fortunately small and they are relatively more prominent at rest than during exercise. Since neither the capacity to exchange maximal volumes of air nor the capacity to distend the lungs to a normal vital capacity are impaired, one would predict that patients with pulmonary insufficiency would tolerate pregnancy without much additional difficulty. The data of normal pregnant women show that the increment of ventilation is relatively constant. This makes it possible to calculate the expected breathing reserve at term for any given patient with pulmonary insufficiency. However, any such calculation is valid only if it can be shown that in patients with diminished lung volume and impaired breathing capacity pregnancy has as little effect on these functions as it has in normal persons. Since respiratory data of patients with pulmonary insufficiency during pregnancy are not available from the literature, a study was undertaken to supply this information. These observations, when completed, will be presented in the third paper of this series (24).

The sensation of difficulty or distress in breathing is not easily evaluated because, as with any other symptom, the examiner has to rely on the patient's verbal report of the sensation.

Shortness of breath on exertion is usually due to an inability to exchange adequate volumes of air during periods of stress. This deficiency may be due to a restriction of the stroke volume or to an obstruction to air flow. In pregnancy there is no restrictive defect, for the vital capacity remains within normal limits. Obstruction is not a factor since the maximal breathing and timed capacities and the air velocity index remain undisturbed (47).

Occasionally, dyspnea is experienced in spite of a normal ventilatory capacity when there is an excessive pulmonary ventilation for particular level of activity. This excessive ventilation is metabolic if it is accompanied by a corresponding increase in oxygen requirement. For example, metabolic hyperpnea may cause dyspnea in severe thyrotoxicosis or leukemia. Metabolic hyperpnea does occur during pregnancy but it is not of sufficient magnitude to explain the marked dyspnea in some subjects. Excessive pulmonary ventilation, not accompanied by an increased demand for oxygen, may be due to pulmonary pathologic changes. It has been suggested in the previous discussion that the hyperpnea of pregnancy

is not due to local pulmonary disturbances but is the response of an increasingly irritable respiratory center. This may explain the early appearance of dyspnea, usually during the second to fifth months. It may also explain the rather unusual complaint of dyspnea at rest without dyspnea during exercise.

Observations of the present subjects suggested that psychologic factors are perhaps as important in relation to dyspnea as measurable changes in pulmonary function. In patients who are short of breath due to pulmonary disease, the symptom almost invariably increases with increasing levels of activity. This is not always true in pregnant women. In lung disease, dyspnea at rest is not usually seen until the resting breathing reserve is less than 70 or 60 per cent. In pregnancy an adequate breathing reserve is maintained throughout and the walking index never reaches the dyspnea level of 35 per cent (50). In patients with pulmonary disease there is usually a good correlation between shortness of breath and objective measures of pulmonary insufficiency (62), and this applies to some extent to patients with dyspnea secondary to heart disease (45). Figure 6 fails to show such a correlation in pregnancy.

One of the more important features leading to a complaint of dyspnea is the newness of the sensation. The present writers have known patients to complain of dyspnea at rest who had only a minimal unilateral pleural effusion. In contrast, patients some years after pneumonectomy rarely complain of dyspnea. They have become used to the sensation and also have learned to adapt their activity to their pulmonary reserve. Likewise, normal subjects not accustomed to dyspnea are intolerant of the slightest air-way obstruction, while patients with bronchial asthma of many years' duration may not complain of shortness of breath even while struggling to breathe. A gradual acclimatization to the increased ventilatory requirement may explain why a number of the present subjects complained more of dyspnea during the early part of pregnancy. It may be the reason why some subjects complained during the course of pregnancy but failed to acknowledge this fact in the retrospective questionnaire. Also because of this, dyspnea is usually more marked during the first pregnancy.

Relief of dyspnea prior to delivery has been attributed to the descent of the fetal head into the pelvis. Four of the subjects did feel relieved after this had occurred. The respiratory studies failed to show an abatement of hyperpnea or a sudden increase of ventilatory capacity at this time. Two of the 4 patients believed that the improvement they observed at the time of engagement was not truly a relief from dyspnea but rather a lessened abdominal tension and a greater ability to move about. This self-analysis suggests another cause for the difficulty of pregnant women in maintaining their activities during the later months. They have a sense of imbalance and fatigue, which contributes to the total complex of dyspnea. The present group of patients was too small and the original questions concerning dyspnea were not sufficiently specific for a more detailed analysis of these factors.

Much remains to be determined about the relation of psychologic, sociologic, and environmental factors to dyspnea. Given the opportunity to measure pul-

monary function in a large number of patients, the present writers have been impressed by the great importance which these elements play in the complaint of dyspnea, particularly during the course of pregnancy.

SUMMARY

Nineteen normal women were studied at intervals throughout pregnancy, early post partum, and six months after delivery to evaluate changes in pulmonary function due to pregnancy.

The most striking alteration was a marked increase of ventilation at rest which could be detected as early as the first trimester and amounted to 42 per cent at term. The oxygen requirement increased later and the increment was never as large as that of ventilation. Both oxygen uptake and ventilation increased out of proportion to weight and body surface.

During exercise, hyperventilation did not occur until the sixth month and at term the exercise ventilatory requirement was 30 per cent greater than during the control period. The resting breathing reserve did not decrease below 85 per cent and the walking dyspnea index never rose above 29 per cent in any individual subject.

Dynamic ventilatory studies, including the maximum breathing capacity, the air velocity index, and the timed capacities, remained within normal limits.

The lung volume profile was not affected until the second half of pregnancy. A fairly constant decrease of the expiratory reserve and the residual volume resulted in an 18 per cent diminution of the functional residual capacity. This volume was lower at term than during the control period in every single subject. The volumetric loss of the expiratory reserve was compensated for by a corresponding rise of the inspiratory capacity. Consequently, the vital capacity remained essentially unchanged in both the upright and supine positions. The total lung capacity was very slightly diminished at term.

Intrapulmonary mixing studies revealed no defect of gaseous distribution at any time during pregnancy.

The early postpartum period should not be used as a control in evaluating functional alterations during pregnancy since increased oxygen uptake and ventilation persisted for some weeks after delivery. Also, the early postpartum period was the only time when a marked reduction of vital capacity, total lung capacity, and maximum breathing capacity could be demonstrated.

In individual subjects no correlation was found between measurable alterations of pulmonary function and the severity of dyspnea during pregnancy.

The possible effects of these physiologic alterations on coexisting pulmonary tuberculosis were considered. The constant and significant reduction of the functional residual capacity may favorably influence the course of the disease while the increased ventilatory demand may have an adverse effect.

SUMARIO

La Función Pulmonar en el Embarazo. I. Observaciones Seriadas en Mujeres Normales

Diecinueve mujeres normales fueron estudiadas a ciertos intervalos durante el embarazo, los principios del puerperio y seis meses después del parto para determinar las variaciones de la función pulmonar debidas al embarazo.

La alteración más notable consistió en un notable aumento de la ventilación en reposo, que ya era distinguible desde el primer trimestre y que representaba 42 por ciento a término. Los requisitos de oxígeno aumentaron después, pero el incremento no fué nunca tan grande como el de la ventilación. El aumento tanto de la toma de oxígeno como de la ventilación no guardó relación con el peso o la superficie del cuerpo.

Durante el ejercicio, no se presentó hiperventilación hasta el sexto mes y a término el requisito ventilatorio durante el ejercicio fué 30 por ciento mayor que durante el período de control. La reserva respiratoria en reposo no descendió a menos de 85 por ciento y el índice de disnea ambulante jamás se elevó a más de 29 por ciento en ningún sujeto dado.

Los estudios de la dinámica ventilatoria, comprendiendo la capacidad respiratoria máxima, el índice de velocidad del aire y las capacidades por minuto, revelaron límites normales.

El perfil del volumen pulmonar no se afectó hasta la segunda mitad del embarazo. Una disminución bastante constante de la reserva expiratoria y del volumen residual dió por resultado una baja de la capacidad residual funcional. Dicho volumen fué más bajo a término que durante el período de estudio en todas las mujeres del grupo. La pérdida volumétrica de la reserva expiratoria fué compensada por un alza correspondiente de la capacidad inspiratoria. Por consiguiente, la capacidad vital permaneció substancialmente inalterada en las posiciones tanto erecta como supina. La capacidad pulmonar total reveló ligerísima disminución a término.

Los estudios del intercambio intrapulmonar mo revelaron deficiencia de la distribución gaseosa en ninguna ocasión durante el embarazo.

El período puerperal incipiente no debe ser utilizado como índice para determinar las alteraciones funcionales durante el embarazo, dado que el aumento en la toma de oxígeno y en la ventilación continuó por algunas semanas después del parto. Además, ese periodo fué el único en que pudiera observarse notable reducción de la capacidad vital, la capacidad pulmonar total y la capacidad respiratoria máxima.

En las distintas mujeres, no se descubrió correlación entre las alteraciones mensurables de la función pulmonar y la intensidad de la disnea durante la gestación.

Consideráronse los posibles efectos de esas alteraciones fisiológicas sobre una tuberculosis pulmonar coexistente. La constante e importante reducción de la capacidad residual funcional puede afectar favorablemente la evolución de la enfermedad, mientras que puede ejercer efecto adverso el aumento de los requisitos ventilatorios.

RESUME

La fonction pulmonaire dans la grossesse: I. Observations en série chez des femmes normales

Dix-neuf femmes normales ont été étudiées périodiquement pendant la grossesse, au début du post-partum et six mois après l'accouchement, dans le but de déterminer les modifications de la fonction pulmonaire résultant de la grossesse.

La modification la plus frappante a été un accroissement de la ventilation au repos, qui pouvait être découverte dès le premier trimestre et atteignait 42 pour cent à terme. Les besoins en oxygène augmentaient plus tard; cet accroissement n'était jamais aussi élevé que celui de la ventilation. L'augmentation de la consommation d'oxygène et celle de la ventilation n'étaient pas proportionnelles au poids et la surface du corps.

Au cours de l'exercice, l'hyperventilation ne se produisait pas avant le sixième mois et, à terme, les besoins de ventilation dans l'exercice étaient supérieurs de 30 pour cent à ceux de la période de contrôle. Au repos, la réserve respiratoire ne s'abaissait pas au-dessous de 85 pour cent et l'indice de dyspnée à la marche n'a jamais dépassé 29 pour cent dans aucun cas individuel.

Les résultats des études de ventilation dynamique, y compris la capacité respiratoire maxima, l'indice de vélocité de l'air et les capacités dans le temps, sont restés dans les limites normales.

Jusqu'à la deuxième moitié de la grossesse le volume du poumon n'était pas affecté. Une réduction assez constante de la réserve expiratoire et du volume résiduel a amené une

diminution de 18 pour cent dans la capacité résiduelle fonctionnelle. Chez chaque sujet, ce volume était plus bas à terme que pendant la période de contrôle. La perte volumétrique de la réserve expiratoire était compensée par une élévation correspondante de la capacité inspiratoire. En conséquence, la capacité vitale est demeurée essentiellement inchangée dans la position debout comme dans la position couchée. La capacité totale du poumon était trés légèrement diminuée au terme de la grossesse.

A aucun moment de la grossesse, l'étude du mélange gazeux intrapulmonaire n'a révélé aucune altération de la répartition des gaz.

Le début de la période post-partum ne doit pas être utilisé comme témoin dans l'évaluation des altérations fonctionnelles au cours de la grossesse, car l'accroissement de la consommation d'oxygène et de la ventilation persistait pendant plusieurs semaines après l'accouchement. De plus, la période post-partum initiale était le seul moment où il était possible de démontrer une réduction marquée de la capacité vitale, de la capacité pulmonaire totale et de la capacité respiratoire maxima.

L'étude de cas individuels n'a pas permis d'établir une corrélation entre les altérations mesurables de la fonction pulmonaire et la sévérité de la dyspnée, au cours de la grossesse.

Le retentissement possible de ces modifications physiologiques sur la tuberculose pulmonaire coexistante est étudié. La réduction constante et significative de la capacité résiduelle fonctionnelle peut influencer favorablement le cours de la maladie, tandis que le besoin d'une ventilation accrue peut avoir un effet inverse.

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A COMPARATIVE STUDY OF THE EFFECTIVENESS OF LARYNGEAL SWABS AND GASTRIC ASPIRATION FOR THE DETECTION OF M. TUBERCULOSIS IN CHEST CLINIC PATIENTS[1]

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INTRODUCTION

The laryngeal swab technique for the detection of *M. tuberculosis*, originally described more than forty-five years ago (1), has been increasingly adopted during the past decade with almost unanimous agreement on its advantages over gastric aspiration, particularly for outpatients (2–12).

In view of these reports, the present writers attempted to find out if there was a place for this technique in the twenty-three chest clinics operated by the Bureau of Tuberculosis, City Health Department, under conditions not approximated in any of the previous investigations. A special study was therefore started in December, 1950, to determine the relative efficacy of laryngeal swabs and gastric aspiration for the detection of *M. tuberculosis* under the following conditions peculiar to this Bureau:

(*a*) A large number of clinics, with frequently changing personnel inexperienced in the laryngeal swab technique, would be employed.

(*b*) There would be a delay of at least twenty-four hours from the time a specimen would be collected to the time it would be cultured.

(*c*) Specimens would be transported for considerable distances at room temperature.

(*d*) A single central laboratory would be used for the examination of the specimens.

METHODS OF STUDY

Selection of Material

The study was conducted from December, 1950, to June, 1952, in eleven clinics selected at random. All patients for whom gastric aspirations were ordered had laryngeal swabs taken immediately prior to the aspirations. The indications for gastric aspiration were the usual ones for chest clinic patients who cannot or will not raise a satisfactory sputum specimen.

During the period of study, 1,434 combined sets of specimens were collected. Of these, 16 were eliminated because of contamination; the gastric specimen being involved 14 times, and the laryngeal swabs twice. The remaining 1,418 combined sets of specimens form the basis of the study.

Collection of Specimens

Each patient reported to the clinic without breakfast and after variable travel times. Specimens were collected between 9:00 and 10:00 a.m. A clinic physician

[1] From the Bureaus of Tuberculosis and Laboratories, Department of Health, 125 Worth Street, New York 13, New York.

first obtained two laryngeal swabs, placing each into a separate tube, and then did a gastric aspiration, putting the contents into a dry sterile bottle. The two tubes with the swabs and the bottle of gastric contents for each patient were then bound together firmly and sent to the laboratory as a single unit by messenger service. All specimens were subsequently cultured in the central laboratory of the Bureau of Laboratories twenty-four hours later. Wherever possible, the specimens were kept in a refrigerator but, for much of the interval from the time of collection to the time of culture, they were kept at room temperature. None of the material from the laryngeal swabs or gastric contents was submitted for microscopic examination.

Laryngeal Swab Technique

Materials:

Laryngeal swabs made from 9-inch lengths of malleable 18-gauge wire of chrome-nickel alloy, to one end of which a pledget of absorbent cotton was fastened by collodion; a large loop was made at the other end. Swabs were sterilized in dry test tubes and were delivered to the clinics.

Sterile test tubes containing 2 cc. of 10 per cent $Na_3 PO_4$ 0.12 H_2O and sealed with aluminum foil-covered corks.

Narrow-mouthed bottles of sterile distilled water.

Cotton gauze squares.

Celluloid masks made of discarded X-ray film to cover the entire face. They were sterilized chemically.

Technique: The laryngeal swab was first placed in the bottle of sterile distilled water to moisten the cotton thoroughly. The applicator was then partially withdrawn until a point two inches from the cotton tip was on a level with the mouth of the bottle. At this point, the applicator was bent against the mouth of the bottle to form a 45-degree angle and was then ready to use. While the patient's tongue was firmly pulled forward and held in this position,[2] an attempt was made to direct the swab blindly into the larynx by closely following the curve of the base of the tongue and avoiding, as much as possible, contact with the mucous membranes of the mouth or pharynx. As has been noted elsewhere (9), such a swab, in most instances, reaches some part of the hypopharynx rather than the larynx, although the latter should always be considered the objective. If this maneuver did not elicit a cough, the patient was then asked to cough several times against the swab. In this way, the swab had a better chance of being bathed adequately in the laryngeal secretions. More recently, the patient has been directed to cough several times, without swallowing or expectorating, *before* as well as *after* introducing the swab in order to increase the secretions in the region of the larynx and the hypopharynx. After the swab had been adequately exposed to the secretions, it was removed and then submerged in the trisodium phosphate solution in the specially provided carrying tube. As the swab was placed into the test tube, the bent applicator straightened itself out. The test tube was then carefully sealed by means of the aluminum foil-covered cork, with the protruding wire applicator tightly squeezed between the cork and the side of the tube. A second swab was then collected in identical fashion and both

[2] Dentures, if present, should be removed.

carrying tubes with the submerged swabs were sent, in an upright position, to the laboratory where cultures were made twenty-four hours later.

This technique was found very well suited for outpatient service. Both nurses and physicians found the taking of laryngeal swabs much more convenient and less time-consuming than the extraction of gastric contents. As for the patients, almost without exception they much preferred having their throats swabbed to swallowing the gastric tube.

Culturing Methods

Gastric contents: As soon as the gastric specimens were received in the laboratory, they were placed in a refrigerator and kept there overnight. The following morning the contents were treated with an equal volume of 4 per cent sodium hydroxide, agitated for five minutes on a Kahn shaking machine, and then allowed to remain at room temperature for twenty minutes; the treated contents were then neutralized with normal hydrochloric acid, using phenolphthalein as an indicator. The neutralized specimen was centrifuged at 4,000 r.p.m. for twenty minutes, and the supernatant fluid was decanted. Approximately 0.5 cc. of sterile distilled water was used to resuspend the sediment, which was then inoculated into two tubes of medium[3] by means of small sterile cotton swabs. The tubes were incubated at 37°C. and observed biweekly for six weeks.

Laryngeal swabs: Several methods of treating the laryngeal swabs, including those described in the literature (8–12), were attempted. After considerable experimentation, the following method was adopted as the most sensitive under the conditions of this study:

The two carrying tubes containing the swabs submerged in the trisodium phosphate solution were agitated on a Kahn shaking machine for thirty minutes. Each swab was then removed and streaked on two tubes of medium.[3] The liquid in the tube was centrifuged, the supernatant carefully decanted, and the precipitate transferred by means of a capillary pipette to two additional tubes of medium.[3] The inoculated cultures were then incubated at 37°C. and read at biweekly intervals for six weeks.

Examination of cultures: If either the gastric specimen or both laryngeal swabs were contaminated, the entire set of specimens was eliminated from the study. If only one of the two swabs was contaminated, the combined set of specimens was included.

The culture, from either the swab or gastric contents, was considered positive if any characteristic growth, even a single colony, was present. All cultures positive for *M. tuberculosis* were checked by smear and, if the morphology of the acid-fast organisms was found to be atypical, the colonies were subcultured and injected into guinea pigs for confirmation of the presence of *M. tuberculosis*. In reporting the results of the cultures of the laryngeal swabs, both swabs were considered as a unit, so that a positive result would be recorded whether growth developed from one or both specimens.[4]

RESULTS

In table 1 are listed the results of the cultures for *M. tuberculosis* made from the combined sets of specimens of the 1,418 patients included in the study. A total of 207 cases, or almost 15 per cent of the series, had cultures positive for *M. tuberculosis* from the gastric contents, from the laryngeal swabs, or from both sources. Approximately 90 per cent (187) of the cases with "positive" cultures were identified by gastric aspiration, whereas only 65 per cent (135) of the

[3] One tube of Jensen's modification of Löwenstein's medium and one tube of Peizer-Schecter agar medium (13).

[4] Of the 135 instances in which the laryngeal swabs were reported as positive, 62 were on the basis of positive cultures isolated from both swabs, and 73 on the basis of positive cultures from just a single swab.

"positives" were identified by culture of the swabs. Thus, two laryngeal swabs taken at the same time proved to be approximately 72 per cent as effective as a single gastric aspiration for the detection of *M. tuberculosis*.

TABLE 1

RESULTS OF CULTURES FOR M. TUBERCULOSIS FROM CONCOMITANTLY OBTAINED GASTRIC ASPIRATIONS AND LARYNGEAL SWABS

RESULTS AND METHODS	NUMBER	PER CENT OF COMBINED SETS OF SPECIMENS	PER CENT OF TOTAL NUMBER OF POSITIVES
Negative on gastric contents and laryngeal swabs	1,211	85.4	—
Positive on:			
Gastric contents, or laryngeal swabs, or both	207	14.6	100.0
Both gastric contents and laryngeal swabs	115	8.1	55.6
Gastric contents only	72	5.1	34.8
Laryngeal swabs only	20	1.4	9.6
Total	1,418	100.0	—

COMMENT

Under the conditions of this study, two concomitantly obtained laryngeal swabs were significantly inferior to a single gastric aspiration as a source material for the culture of tubercle bacilli. Thus, in spite of the conveniences of the swab technique in the clinic, gastric aspiration remains the method of choice for the detection of *M. tuberculosis* in the present clinics for patients who are unable to produce an adequate sputum specimen.

With added experience, the swab technique may be found sufficiently efficacious under all conditions to warrant supplanting gastric aspiration in many of the clinics in this country as it has done in England. Until that time, as a tool for the bacteriologic diagnosis of tuberculosis in outpatients, the laryngeal swab technique can serve as a valuable alternative to gastric aspiration, to be used in special circumstances. Among the situations in which use of the technique might be appropriate are those in which patients refuse to swallow, or cannot swallow, a gastric tube; in which patients cannot, or will not, report to the clinic in the morning without breakfast;[5] or in which a delay of more than twenty-four hours is anticipated before the specimen can be cultured.[6]

[5] Laryngeal swabs may be collected at any time of day, before or after meals, without altering the efficacy of the technique. This observation, while not confirmed by the present writers, has, nevertheless, been well established by other investigators (4–10).

[6] The present writers have not found it practicable to add a buffering agent to gastric specimens at the time they are collected. Such agents have been reported as delaying the deterioration of gastric contents (10, 14). Without such agents, there is a marked fall in the number of viable organisms present in the gastric contents after twenty-four hours. On the other hand, the present writers have found no significant loss of viability in laryngeal swabs allowed to stand submerged in trisodium phosphate at room temperature up to seventy-two hours (15).

It may also be possible to use the swab technique as a screening procedure preliminary to gastric aspiration. For instance, in some clinics it may prove to be practicable and worth while to institute a routine of preceding each gastric aspiration with a set or two of laryngeal swabs and to use the gastric method only when the swabs have been found to be negative for tubercle bacilli.

SUMMARY

Two laryngeal swabs were taken concomitantly with an aspiration of gastric contents in 1,418 chest clinic patients for whom the latter procedure was indicated. Cultures for *M. tuberculosis* were prepared twenty-four hours later. Positive cultures, by one or both of the methods, were found in 207 cases. Of these, 187 (90 per cent) showed growth from the gastric contents, and 135 (65 per cent) from the swabs. Thus, under the conditions of this study, a set of swabs was only 72 per cent as effective as gastric aspiration for detecting *M. tuberculosis* in chest clinic patients.

The laryngeal swab technique is worthy of adoption as an additional diagnostic tool for the bacteriologic diagnosis of tuberculosis in ambulatory patients to be used when gastric aspiration cannot readily be performed.

SUMARIO

Estudio Comparado de la Eficacia de los Frotes Laríngeos y de la Aspiración Gástrica para el Descubrimiento del Mycobacterium Tuberculosis en los Enfermos de una Clínica Torácica

Obtuviéronse dos ejemplares laríngeos en torundas de algondón junto con la aspiración del contenido gástrico en 1,418 enfermos de una clínica para enfermedades del tórax, en quienes estaba indicado el último procedimiento. Se prepararon cultivos para el *M. tuberculosis* veinticuatro horas después. En 207 casos, se consiguieron resultados positivos con una de las dos técnicas o con ambas. De ellos, 187 (90 por ciento) revelaron colonias procedentes del contenido gástrico y 135 (65 por ciento) de los frotes laríngeos. En las condiciones de este estudio, un juego de frotes reveló, pues, solamente 72 por ciento de eficacia, comparado con la aspiración gástrica, en lo tocante al descubrimiento del *M. tuberculosis* en los enfermos de la clínica.

La técnica de los frotes laríngeos es digna de empleo como otra arma de diagnóstico para el diagnóstico bacteriológico de la tuberculosis en los enfermos ambulantes, para uso en situaciones en que no cabe ejecutar fácilmente la aspiración gástrica.

RESUME

Etude comparative de l'efficacité du prélèvement laryngé et du tubage gastrique pour la découverte du Mycobacterium tuberculosis chez des malades de cliniques du poumon

Deux prélèvements laryngés et une aspiration du contenu gastrique ont été pratiqués simultanément chez 1.418 malades de cliniques du poumon pour lesquels l'examen bactériologique était indiqué. Les cultures pour le *M. tuberculosis* étaient entreprises vingt-quatre heures plus tard. Des résultats positifs par une de ces méthodes, ou par les deux réunies, ont été obtenus dans 207 cas. Sur ce nombre, 187 (90%) ont permis d'obtenir des cultures à partir du contenu gastrique et 135 (65%) à partir des prélèvements laryngés. Donc, dans les conditions de l'étude une série de prélèvements laryngés n'a été efficace que dans la proportion de 72% par rapport à l'aspiration du contenu gastrique pour déceler le *M. tuberculosis* chez les malades des cliniques de la tuberculose.

La technique du prélèvement laryngé mérite d'être adoptée comme instrument additionnel pour le diagnostic bactériologique chez les malades des consultations externes, dans les cas où le tubage gastrique est difficilement réalisable.

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A ROENTGENOGRAPHIC CLASSIFICATION OF TUBERCULOUS LESIONS OF THE KIDNEY[1,2]

JOHN K. LATTIMER

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INTRODUCTION

Accurate comparisons of the effectiveness of new antituberculosis drugs will not be possible until better standards are established by which results can be judged. It is futile to compare percentages of bacteriologic "conversions" among patients who have massive necrotic kidney lesions (figure 1*A*) with those of patients who have only tiny lesions of the kidney (figure 1*B*). Yet in the past, before the advent of the new drugs made more accurate reporting necessary, few attempts were made to differentiate between the various sizes of lesions which were the targets for therapy.

The need for a standardized, accurate classification of the kidney lesions is particularly urgent in view of the small numbers of patients who can be treated and studied in the intervals before even newer drugs are discovered and the plan of treatment altered. The purpose of this paper, therefore, is to present a roentgenographic classification of tuberculous kidney lesions which has been worked out and used by the Research Unit for Genito-Urinary Tuberculosis at the Kingsbridge Veterans Hospital in New York City, and at Columbia University, during the past six years. This method of classifying clinical material has proved satisfactory to date. The vulnerability to criticism of data based on shadows cast, or not cast, on roentgenographic films has been recognized, and efforts have been made to minimize it.

Definite proof of tuberculosis, such as a urine culture positive for *M. tuberculosis*, a positive guinea pig test, or positive histologic evidence after surgery, was demanded in all cases used in these research studies. Smears positive for acid-fast bacilli were not accepted for research purposes, although in clinical practice the presence of a positive smear together with classical roentgenographic signs of the disease might be considered sufficient grounds on which to initiate treatment. The isolation of *M. tuberculosis* on culture of the urine collected from the ureter was required of patients with equivocal roentgenographic changes, and was preferred in all cases. Treatment was sometimes started, however, on the basis of definite roentgenographic changes in the kidney and a positive culture from the voided urine. As soon as the diagnosis was established bacteriologically, the extent of the kidney lesion was estimated from the roentgenographic findings.

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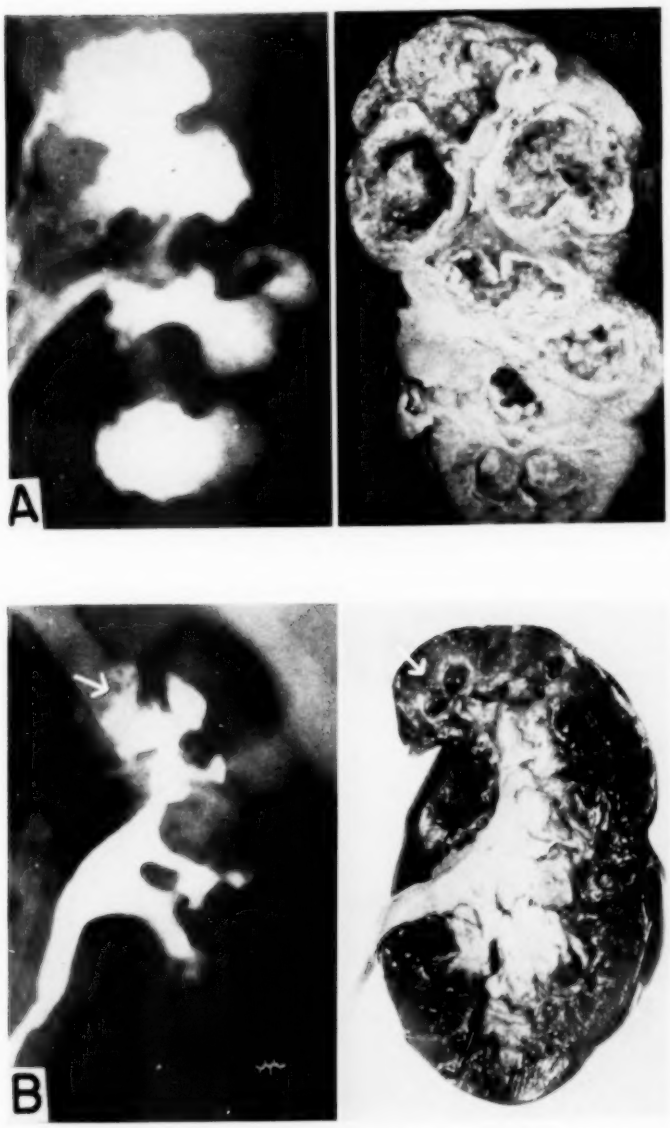

FIG. 1. It would be futile to compare the effects of two new drugs if one were tested on massive tuberculous lesions of type A (above), while the other was tested on small lesions of type B (below).

DESCRIPTION OF CLASSIFICATION METHODS

Multiple (6 films) retrograde pyelograms were done as gently as possible, in several positions, with injection of no more than 3 to 5 cc. of 40 per cent Skiodan at one time. Five cubic centimeter aliquots of urine were collected in graduated centrifuge tubes under as closely similar conditions of moderate diuresis as possible, so that the number of leukocytes per high-power field could be compared at the time of each cystoscopy. From 20 to 100 cc. of urine were also collected from each ureteral catheter in sterile centrifuge tubes to be cultured for tubercle bacilli at each examination. The same observer performed all cystoscopies and interpreted all roentgenograms during the six-year period. Excretion urograms were also done on all patients. They sometimes showed a cavity in the parenchyma of the kidney which was not visualized in the retrograde pyelograms.

CLASSIFICATION

The kidney lesions were classified into five different groups, according to the extent of the visible tuberculous changes.

Group 0: Group 0 was made up of kidneys which showed no pyelographic abnormalities whatsoever (figure 2, *Group 0*). All kidneys of *Group 0* discharged pus cells and had been proved to be tuberculous by the culturing of tubercle bacilli from the ureteral specimens. Moreover, fair evidence exists that the presence of tubercle bacilli and pus cells in the urine indicates the presence of small discharging lesions. Hence, it was assumed that the lesions in this group were too tiny to be visualized even in multiple pyelograms. They may well have been the type of early blood-borne parenchymal lesions which had not yet become fibrous or caverno-caseous. The smaller extent and the absence of fibrous and necrotic tissue in this type of lesion might make it heal more easily than the more obvious caverno-caseous lesions. Meyer of Copenhagen (2) has shown that a certain percentage of lesions of this type may heal spontaneously even without chemotherapy. Because of this definitely better prognosis, therefore, it was thought best to designate this group as *Group 0*, and thus set it apart from *Groups 1*, *2*, *3*, and *4*, which probably represented progressive stages of the caverno-caseous type of lesion.

The possibility that *Group 0* also included some large lesions in which communication with the pelvis or calyces had been closed off by strictures could not be completely ruled out. It was observed, however, that, after at least six different retrograde pyelograms and three different excretion pyelograms had been made during the diagnostic studies, it was usually possible to detect any large lesions. If large lesions were found after surgery or at necropsy, which made it apparent that the kidney should not have been included in *Group 0* even when first seen, the patient's classification was changed from *Group 0* into the appropriate *Group 1*, *2*, *3*, or *4*.

Group 1: Group 1 consisted of those patients who showed a slight but definite roentgenographic abnormality of the pelvis, calyces, or upper ureter. These changes were insufficient to be diagnosed as "typical" of tuberculosis. This category was thought necessary because even slight visible alterations usually were associated with extensive involvement of kidney tissue, all out of proportion to the minimal deformity detectable by roentgenography (figure 2, *Group 1*).

Kidneys without visible calyceal changes, but which showed persistent deformities of the pelvis or ureter, were placed in *Group 1*. It was believed that such deformities resulted from the discharge of large numbers of tubercle bacilli or from long-standing infection and, therefore were indicative of larger lesions than those of *Group 0*, even though cavities were not visualized by pyelography.

A ROENTGEN CLASSIFICATION OF TUBERCULOUS KIDNEY LESIONS

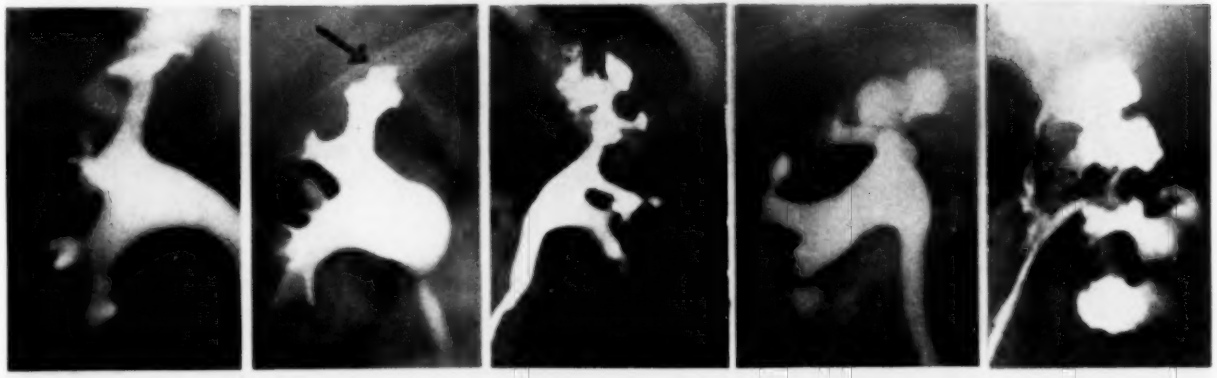

FIG. 2. All kidneys had urine cultures positive for tubercle bacilli. *Group 0* (left) showed no roentgenographic changes. *Group 1* showed atypical changes. *Groups 1, 2, 3,* and *4* were interpreted as progressive stages of caverno-caseous renal disease. The chances for failure with chemotherapy appeared to vary directly with the extent of the disease.

Group 2: Kidneys proved to be tuberculous which showed a distortion of as little as a single minor calyx, but with a roentgenographic appearance typical of tuberculosis, were placed in *Group 2* (figure 2, *Group 2*).

Group 3: Tuberculous kidneys, roentgenograms of which showed two characteristically altered calyces or two large areas of involvement, such as cavitations, calcifications, or segments of nonfunctioning parenchyma, constituted *Group 3* (figure 2, *Group 3*).

Group 4: Kidneys, roentgenograms of which showed massive tuberculous lesions involving three or more calyces, were placed in *Group 4* (figure 2, *Group 4*). "Putty" kidneys with positive urines fell into this group.

0	NO ROENTGEN ABNORMALITY VISIBLE BUT URETERAL URINE POSITIVE FOR TUBERCLE BACILLI	SMALL RENAL LESIONS	0
1	DEFINITE SLIGHT ROENTGEN ABNORMALITY, BUT NOT DIAGNOSTIC FOR TUBERCULOSIS, INCLUDES DOUBTFUL CALYCEAL DISTORTIONS, AND SLIGHT BUT DEFINITE IRREGULARITIES OF THE PELVIS OR UPPER URETER. URETERAL URINE POSITIVE FOR TUBERCLE BACILLI.	MEDIUM SIZED RENAL LESIONS	1
2	ONE CALYX ONLY, WITH DEFINITE ROENTGEN CHANGES CHARACTERISTIC OF TUBERCULOSIS. URETERAL OR VOIDED URINE CULTURE POSITIVE.		2
3	TWO CALYCES SHOWING THE DISTORTIONS OF TUBERCULOSIS URETERAL OR VOIDED URINE CULTURE POSITIVE.	LARGE RENAL LESIONS	3
4	THREE OR MORE CALYCES OBVIOUSLY TUBERCULOUS BY X-RAY. URETERAL OR VOIDED URINE CULTURE POSITIVE. MASSIVE PUTTY TYPE LESIONS IN THIS CATEGORY.		4

FIG. 3. A roentgenographic classification of tuberculous kidney lesions.

Calcification

The presence of calcification did not change the assignment of any lesion to its proper size category. The presence of calcium did eliminate the kidney from either *Group 0* or *Group 1*, each of which was composed of kidneys with insufficient roentgenographic signs to indicate the exact location or type of the tuberculous lesion. The presence of calcification was prominently recorded, however, in addition to the extent of the lesion since calcium appeared to indicate the presence of necrotic tissue which inhibited healing by chemotherapy alone. Calcification did not indicate that a lesion was necessarily either old or extensive.

Hydronephrotic Kidneys

Hydronephrosis and hydroureter resulting either from tuberculous stricture of the lower ureter or from reflux up through a diseased uretero-vesical junction sometimes made proper classification difficult. It was necessary to correct the condition which caused the "back pressure kidney" before a true estimate of the size of the tuberculous renal lesion could be determined. False diagnoses of renal tuberculosis were sometimes caused by reflux, since bladder urine, contaminated with tubercle bacilli from the prostate or the other kidney, could be pushed up to the pelvis and there collected by ureteral catheter. Such questionably infected kidneys were not acceptable for research purposes.

"Excluded" Lesions

The problem arose of the proper roentgenographic classification of kidney lesions in which the tuberculous process was completely "excluded" from the

remainder of the kidney by scarring and fibrosis. This uncertainty also applied to the "putty" kidney. These difficulties arose infrequently because, if the lesion was truly isolated by stricturing of the calyx or ureter, tubercle bacilli were not found in the urine and, as a result, the diagnosis could rarely be established. It was observed that most lesions which appeared to be isolated were usually discharging tubercle bacilli into the urine intermittently. It appeared logical to assign these massive lesions, which were obvious by roentgenography, to *Group 3* or *Group 4* according to their actual size if *M. tuberculosis* could be cultured from ureteral urine.

Significance of Symptoms

Symptoms were not reliable in estimating either the size or age of the renal lesion. Fifty per cent of the writer's patients with viable tubercle bacilli in the urine and lesions of various sizes in their kidneys had no symptoms, either in the form of bladder dysfunction or lumbar pain. Routine medical examinations of these young veterans who were applying for employment after release from the Army led to this high discovery of asymptomatic cases.

Criteria of Arrest

The necessarily strict criteria on which to base statements on the arrest of the disease were also considered. After the end of each course of chemotherapy, a period of three months was allowed in order to eliminate any question of temporary "conversions" due to residual chemotherapeutic agents in the tissues. It was found, as suggested by Lunggren, that isoniazid suppressed the growth of tubercle bacilli in the urine for five days after therapy was stopped. Nine consecutive twenty-four-hour urine concentrates were examined by culture at least every six months for a five-year period. All had to be negative for *M. tuberculosis*. Cystoscopic examinations were performed at least every six months over the course of five years. Urine collected from ureteral catheters at these examinations sometimes showed cultures and guinea pig inoculations negative for tubercle bacilli, while cultures of the voided urine were positive. These findings were often the result of infections in the prostate gland. In these patients, it was required that both the voided urine and the ureteral urine be negative for tubercle bacilli for five years after termination of treatment before the kidney lesion was declared arrested. Cultures of the semen for tubercle bacilli were also made.

DISCUSSION

It is apparent that the patients in *Group 0* represent a category by themselves, in which the prognosis was relatively favorable even before the advent of chemotherapy. It is also probable that the number of infections detected in this early "minimal" stage will always be small. In the writer's experience, the *Group 0* lesions are usually found by physicians who are watching the contralateral "good" kidney after the removal of a tuberculous kidney on the other side. *Group 0* lesions are also discovered by diligent physicians who look for pus cells

or tubercle bacilli in the urines of all patients with tuberculosis of any kind, especially those with bone and joint disease.

It is also apparent that the patients with lesions in *Groups 1* and *2* made up an important category, wherein the lesion was sufficiently small that the prognosis for arrest through chemotherapy was more favorable than for those with massive lesions. These two groups (*Groups 1* and *2*) together comprised a category of "medium-sized" (moderately advanced) lesions.

The patients in *Groups 3* and *4* constitute the category of "large" renal lesions. They have massive kidney involvement with large amounts of necrotic tissue and, hence, a much poorer prognosis for arrest through chemotherapy. In the

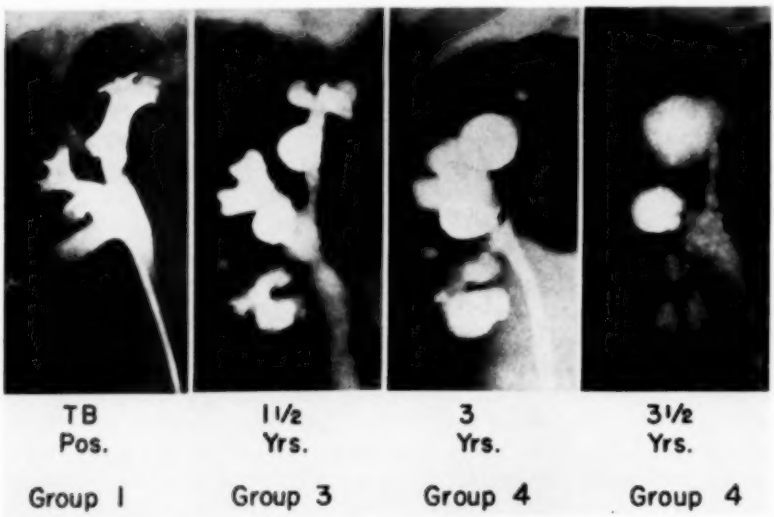

FIG. 4. Progression rates of the disease vary from patient to patient. This 30-year-old man's tuberculous kidney deteriorated rapidly, going from *Group 1* to *Group 4* in three years. Most kidneys deteriorate more slowly.

writer's experience, none of these "far advanced" kidneys with massive lesions has secreted urine consistently negative for *M. tuberculosis* by culture for a five-year period. In some instances, however, it has not been possible to culture tubercle bacilli for periods as long as two years. It is to be hoped that, as newer and more potent combinations of antituberculous drugs are introduced, better results may be obtained with these extensive lesions. For instance, streptomycin plus para-aminosalicylic acid (PAS), given for one year, have already brought about a higher percentage of disappearance of *M. tuberculosis* from the urine than did streptomycin alone.

The classification of kidney lesions as to size has been made, independent of any classification based on the duration of the renal disease. It was noted that the progression rate of renal lesions is unpredictable and varies greatly

from patient to patient (figure 4). In general, however, the disease progresses slowly in young adults, requiring, unless arrested, three to twenty years to destroy the kidney. In contrast, strictures of the ureter could destroy the kidney rapidly.

If all of the criteria employed by each reporter are clearly stated, it will be possible to compare the results of treatment both on the basis of ureteral specimens and voided specimens. It is certainly essential to establish the size of the kidney lesion which is the target for treatment. Thus, the present classification will supplement those of Jacobs and the British Medical Research Council, which classify the patients with unilateral disease, bilateral disease, et cetera. Another notation should always be made of the likelihood of the prostate gland's being the source of the tubercle bacilli in the urine. It is well established that the presence of genital tuberculosis adversely influences the prognosis of patients with renal tuberculosis.

It is the impression of the writer, after six years of experience with antituberculosis drugs, that kidney lesions large enough to be definitely visible by roentgenography surround themselves with so much necrotic and fibrous tissue as to make complete healing difficult on chemotherapy alone. The chances of failure appear to vary directly with the size of the lesion, as estimated from the roentgenograms. A more precise plan for evaluation of the size of the "target" lesions, as seen on the roentgenograms, has been devised, therefore, so that it will be possible to compare both the preliminary and the end results of different chemotherapeutic regimens with greater accuracy.

SUMMARY

Attempts to compare the effects of new antituberculosis drugs upon kidney lesions which differ tremendously in size would obviously be inaccurate. In an effort to bring some order into this situation, a standardized scale for comparing the size of tuberculous kidney lesions has been devised. Three major classifications are used: small, medium, and large, according to the extent of the changes seen on the roentgenograms. A urine culture or guinea pig inoculation positive for *M. tuberculosis* is required to confirm the diagnosis.

"Small" lesions (*Group 0*) are those showing no roentgenographic changes. "Medium-sized" lesions (*Groups 1* and *2*) show definite mild distortion of the pyelogram, involving at most only one calyx. "Large" lesions (*Groups 3* and *4*) are those involving two or more calyces.

This classification has proved reasonably satisfactory during six years of use at the Research Unit for Genito-Urinary Tuberculosis and at Columbia University.

SUMARIO

Clasificación Roentgenográfica de las Lesiones Tuberculosas del Riñón

Los esfuerzos encaminados a comparar nuevas drogas antituberculosas en su efecto sobre lesiones renales cuyo tamaño discrepa sobremanera darían manifiestamente resultados inexactos. Tratando de introducir algún orden en esa situación, se ha elaborado una escala normalizada para comparar el tamaño de las lesiones tuberculosas del riñón. Utilízanse

tres grandes denominaciones: pequeñas, medianas y grandes, de acuerdo con la extensión de las alteraciones observadas en la radiografía. Para confirmar el diagnóstico, se necesitan un urocultivo o una inoculación en el cobayo positivos para *M. tuberculosis*.

Las lesiones "pequeñas" (Grupo 0) son las que no revelan alteraciones radiográficas. Las "medianas" (Grupos 1 y 2) muestran desfiguración, leve pero bien definida, del pileograma, afectando a lo más un solo cáliz. Lesiones "grandes" (Grupos 3 y 4) son las que comprenden dos o más cálices.

Esa clasificación ha resultado bastante satisfactoria durante los seis años de su empleo en la Unidad de Investigación para Tuberculosis Génito-Urinaria y en la Universidad de Columbia.

RESUME

Classification radiographique des lésions tuberculeuses du rein

De toute évidence, la comparaison de l'action des nouveaux antibiotiques sur les lésions du rein, dont l'importance varie considérablement, donnerait des résultats inexacts. Pour remédier a cette situation et comparer entre elles les dimensions des lésions du rein tuberculeux, il a été élaboré une échelle standard. Trois classifications majeures sont utilisées: petite, moyenne, grande, selon l'étendue des altérations apparentes sur les radiogrammes. La culture de l'urine ou l'inoculation au cobaye positives pour le *M. tuberculosis* est réclamée pour confirmer le diagnostic.

Les lésions "petites" (groupe 0) sont celles où le cliché ne montre pas d'altération. Les lésions "moyennes" (groupe 1e et 2) montrent une déformation nette et légère du pyélogramme, intéressant au plus un seul des calices. Les lésions "larges" (groupes 3 et 4) sont celles où deux ou plusieura calices sont intéressés.

Cette classification s'est montrée suffisamment satisfaisante pendant les six années où elle a été employée au "Research Unit for Genito-urinairy Tuberculosis" et à l'Université Columbia.

Acknowledgments

The advice and encouragement given by Drs. George Cahill, Archie Dean, Ross Golden, and George Fish, as this work progressed, were deeply appreciated, as was the assistance of our secretary, Miss Alfreda Jastremski; head nurse, Lydia Sechler; and medical illustrator, Massy Nakamura.

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TUBERCULOUS MENINGITIS IN THE ADULT[1, 2]

A Review of Sixty Consecutive Streptomycin-Treated Cases

EDGAR ALSOP RILEY[3]

(Received for publication October 20, 1952)

INTRODUCTION

Before the introduction of specific antimicrobial therapy, tuberculous meningitis pursued an almost invariably fatal course of approximately three to five weeks' duration. Since the advent of streptomycin and para-aminosalicylic acid (PAS), a certain optimism has crept into the literature concerning the prognosis of this disease, some workers reporting as high as 70 to 80 per cent of survivals (1–3).

The purpose of the present paper is to review a series of 60 consecutive cases of tuberculous meningitis in adults treated with various regimens of chemotherapy on the Bellevue Hospital Chest Service to determine whether this optimism is justified. All of the patients were treated during the five-year period between early winter of 1946 and the late summer of 1951. No attempt will be made to review completely the extensive literature which has appeared on this subject.

The Bellevue Chest Service is a busy service which is often overcrowded and usually understaffed, particularly with regard to nursing personnel. It is not administered primarily as a research service, and these patients were not part of an organized research program. The patients are cared for by a resident staff, which rotates at intervals through the wards, and by an attending staff which is on service four consecutive months during the year. There is thus some unavoidable and probably undesirable loss of continuity in the direction of medical care.

MATERIAL

The patients upon whom this study is based came usually from unfavorable socioeconomic backgrounds. Terminally ill patients admitted moribund have purposely not been excluded since it was believed that to do so would not be giving a representative picture of the problem in a large general municipal hospital. All patients were treated on the Chest Service although in several instances the diagnosis had been made at other hospitals or on other services at Bellevue and treatment had been initiated before transfer. Prior to September, 1950, the majority of patients received streptomycin; subsequent to that date

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[2] Presented in part before the Medical Session, as part of the *Medical Session on Tuberculosis*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 27, 1952.

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all patients received dihydrostreptomycin. Because of evidence of the possible increased incidence of eighth nerve deafness following dihydrostreptomycin, referred to later, this drug was discontinued in favor of regular streptomycin in August, 1952.

Thirty-eight (63 per cent) of the patients were males; 22 (37 per cent) were females. There were 28 Negroes (47 per cent), 2 Puerto Ricans, 2 Chinese, one Japanese, and 27 (45 per cent) white persons. Thirteen of the Negroes were females; 15 were males. There were 19 white males in the group, compared with only 8 white females, and 17 of these (or 28 per cent of the entire group) were more than forty years old. This fact again emphasizes the problem of active tuberculosis in the middle-aged white male (4).

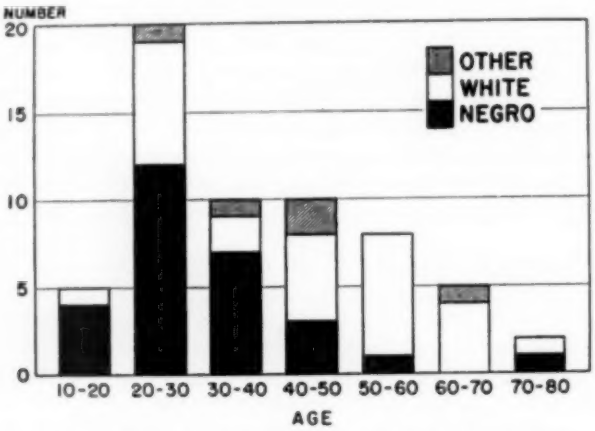

FIG. 1. Chart showing correlation between age and race.

The correlation between age and race is seen in figure 1. The oldest patient in this series was seventy-six; the youngest, fifteen. Although one-third of the patients were in the third decade of life, 25 (40 per cent) were more than forty years old. The ratio of Negro to white patients more than thirty years old shows a striking decrease, reflecting the lower incidence of active tuberculosis found in the older Negro age groups compared with that in white persons of similar age.

Criteria for Diagnosis of Tuberculous Meningitis

The diagnosis of tuberculous meningitis was confirmed bacteriologically in 52 patients (87 per cent) by demonstrating tubercle bacilli in the cerebrospinal fluid either on smear or by culture, or by both methods. In 23 patients (38 per cent), the organism was demonstrated only by culture. Organisms were seen on smear of either centrifugal cerebrospinal fluid or pellicle in only 29 patients.

The frequent difficulty in recovering organisms from the cerebrospinal fluid is a well-established observation. In a composite study, for example, of 450 cases

of tuberculous meningitis treated at various hospitals, it was found that bacteriologic proof was obtained in only 369 (82 per cent) (5).

Five patients in the present study are of particular interest in that organisms resembling *Mycobacterium tuberculosis* were repeatedly seen on smear of the cerebrospinal fluid, in one instance on as many as twelve different examinations, but failed to grow on culture. This phenomenon has also been observed following chemotherapy of pulmonary tuberculosis.

It is not the purpose of the present report to discuss the clinical signs and symptoms or the laboratory findings of tuberculous meningitis in any great detail. Several points, however, are worth emphasis. The diagnosis of tuberculous meningitis in the obscure case may be far from evident and may be overlooked because of the presence of coexisting non-related medical problems. A presumptive diagnosis of tuberculous meningitis can usually be made promptly among the patients with a known history of tuberculosis or among those under treatment for miliary, pulmonary, or localized extrapulmonary forms of the disease. In other circumstances, however, the correct diagnosis may be initially obscure. A list of the various diagnoses originally considered on 17 patients, who were admitted directly to Bellevue either too ill or too mentally confused to give an adequate history or without an antecedent history of tuberculosis, reflects the bizarre forms under which the disease may masquerade. The list includes: cerebrovascular accident (six times); toxic psychosis (six times, several of these patients being admitted directly to the psychiatric service); brain tumor; meningoencephalitis; uremia; subdural hematoma; central nervous system syphilis; carcinomatosis; headache of undetermined etiology; alcoholism; impending delirium tremors; "medical observation"; "surgical observation"; pelvic inflammatory disease; brain abscess; cerebral arteriosclerosis; lymphocytic choriomeningitis; appendicitis; extradural abscess; intestinal obstruction; hyperemesis gravidarum; malignant hypertension; and poliomyelitis.

The characteristic cerebrospinal fluid changes of tuberculous meningitis are well known (6). As the establishment of an unequivocal diagnosis rests upon the initial cerebrospinal fluid findings, it is important to realize that the characteristic "text-book requirements" are not always fulfilled, even in the bacteriologically proved case. In the majority of instances in the present series, the cerebrospinal fluid was clear and colorless on initial examination. In only 2 instances was a typical "ground-glass" appearance mentioned. A pellicle was noted to be present in only 16 cases (27 per cent) although its specific absence was noted only three times. Although an elevated protein content and a low cerebrospinal sugar are characteristic of tuberculous meningitis, several patients had initially low protein and high sugar cerebrospinal fluid values. The occasional finding of a normal or even high cerebrospinal sugar content in tuberculous meningitis, which generally decreases as the disease progresses, has been noted elsewhere (7). It is an extremely useful diagnostic feature of tuberculous meningitis that the cerebrospinal fluid pleocytosis is essentially lymphocytic. Nevertheless, there may be a preponderance of polymorphonuclear leukocytes at the onset (6). Among 13 patients in the present series, an initial differential count of the leukocytes in

the cerebrospinal fluid revealed less than 50 per cent lymphocytes. This ratio invariably increased as the disease advanced. Other laboratory procedures were of no particular diagnostic value.

Treatment Regimens

The various combinations of drugs used in the treatment of meningitis in this group of cases are shown in table 1. Adjunct therapy included bed rest, vitamins, parenteral nourishment, sedatives, and other forms of symptomatic therapy as indicated. There has been some discussion whether therapeutic results justify the intrathecal administration of streptomycin with its attendant complications,

TABLE 1

REGIMENS USED IN TREATMENT OF MENINGITIS IN SIXTY CONSECUTIVE CASES

DRUG COMBINATIONS	NUMBER OF PATIENTS TREATED*	PER CENT
A. Intramuscular and intrathecal streptomycin and/or dihydrostreptomycin	37	62
B. Intramuscular and intrathecal streptomycin and/or dihydrostreptomycin with PAS	13	22
C. Intramuscular streptomycin and/or dihydrostreptomycin with PAS	4	7
D. Intramuscular streptomycin alone	3	5
E. Intramuscular and intrathecal streptomycin, Promizole, and PAS	2	3
F. Intrathecal streptomycin alone	1	1
Total	60	100

* Several patients received additional streptomycin intraventricularly or intracisternally.

the frequent technical difficulties involved, and the severe discomfort suffered by the patient when this method of therapy is continued for long periods of time. Although most workers report better results with combined routes of therapy (5, 8–12), certain investigators (13–15) believe that comparable results are obtained from the intramuscular route alone. Streptomycin will diffuse in higher concentrations across an inflamed than across a normal meningeal membrane. This phenomenon has been used by Lincoln and Kirmse as a test for the early diagnosis of tuberculous meningitis (7) and by the British Medical Research Council for early diagnosis of relapse (9). Two patients demonstrated adequate cerebrospinal fluid streptomycin concentrations on intramuscular medication alone. Nevertheless, 14 patients (23 per cent of the group) developed meningitis while on intramuscular streptomycin therapy, and 4 patients experienced relapse of their meningitis while being maintained on intramuscular medication only. These results form a cogent argument against the use of streptomycin in this disease solely by the intramuscular route.

The variety of dosage regimens followed in this group of patients partly reflects the trial and error basis upon which the optimum dosage schedule for every new drug or combination

of drugs is determined and partly reflects the poor therapeutic results. It is also a reflection of the fact that treatment is often modified by the clinical picture and that a rigid protocol often cannot be strictly followed. Intramuscular streptomycin or dihydrostreptomycin dosage varied from 1 to 3 gm. daily, the majority of patients receiving 1 gm. twice a day. The spacing and individual doses of intrathecal medication were also variable, ranging from 300 mg. daily to 50 mg. every third day. Streptomycin cerebrospinal and blood concentrations studied on one or more occasions on 11 patients showed marked variability with little correlation with the regimens followed. The average dose of PAS was 12 gm. daily.

Drug Toxicity

Toxic reactions to streptomycin therapy, often difficult to distinguish from the effect of the meningeal infection itself, were similar to those described in other series. Deafness is the only one which needs to be considered briefly. Thirteen patients (22 per cent) developed loss of hearing attributable to therapy which ranged from a mild diminution of activity in higher registers to complete deafness. The manifestations of this toxic effect of streptomycin upon the auditory division of the eighth nerve are more liable to be permanent than the manifestations of the toxic effect upon the vestibular division (16). Accumulated evidence shows that auditory loss may be more frequent following the use of dihydrostreptomycin than of streptomycin (17, 18). Although tuberculous involvement of the cochlear portion of the eighth nerve may occur in patients with tuberculous meningitis who become deaf during streptomycin treatment (16), certain workers (19, 20) believe that this effect of dihydrostreptomycin is a contraindication to its use in tuberculous meningitis since no difference has been demonstrated in the therapeutic effects of the two forms of the drug (20, 21).

In the present series, among 15 patients who received dihydrostreptomycin, 4 (26 per cent) developed varying degrees of hearing loss compared with 9 (20 per cent) of the 45 patients who received regular streptomycin. This is not a striking difference but is perhaps made more significant by the fact that the average amount of dihydrostreptomycin given was slightly less than the average amount of regular streptomycin. Reactions following intrathecal medication were not necessarily correlated with high intrathecal dosage. The overall incidence of toxic reactions was not high, probably because of the short duration of illness of many of these patients. In only one instance were these reactions sufficiently severe to warrant discontinuance of therapy. Because of the desperate risk involved, it is only in the exceptionally rare case that premature discontinuation of streptomycin therapy should be considered justified because of toxic complications.

Subarachnoid Block

The serious complication of block, either low in the cord or between the canal and ventricular systems, appeared clinically in 8 patients. The finding of various degrees of hydrocephalus in 12 of the 20 patients examined post mortem indicates that block develops more frequently than is diagnosed clinically. In 4 patients in whom the block developed low in the canal, it was difficult to determine whether the block was secondary to an arachnoiditis produced by streptomycin or whether it was a complication of the meningitis. Cisternal streptomycin therapy was instituted in 3 patients with clinical evidence of block, and in one patient streptomycin was given intraventricularly through frontal burr holes. In one instance block was apparently successfully lysed by the intrathecal use of streptokinase and streptodornase without, however, any appreciable effect upon the general clinical course.

RESULTS

Regardless of the therapeutic regimen employed, the therapeutic results were poor. Three patients (5 per cent) were lost from follow-up observation. There were 4 known survivors (an incidence of 6 per cent) and 53 known deaths (89 per cent).

Forty-nine of the deaths were due to meningitis and complications. Four deaths were nonmeningitic and occurred in patients in whom the meningeal infection was clinically in a period of remission at the time of death. One of these deaths was due to cerebral and subarachnoid hemorrhages secondary to acute myelogenous leukemia, one was due to far advanced bilateral pulmonary tuberculosis, and two were due to extensive hematogenous tuberculosis. Autopsies on two of these patients showed that the meningitis was, temporarily at least, under control, but this is no assurance that these patients would not have succumbed eventually to a relapse. The corrected number of deaths due to active meningitis, 82 per cent, is still high. Forty-eight of these deaths were at Bellevue: five occurred at other hospitals following transfer.

The four survivors were treated on four completely different regimens. Three were Negro females, the fourth was a white male. One has been followed for more than one year, two for almost four years, and the fourth for almost five years. Although three received considerably more streptomycin than the average total dosage of the group as a whole, the fourth patient received a strikingly small amount of drug which, in retrospect, would appear to be wholly inadequate. Two of the four survivors had proved concomitant hematogenous tuberculosis; one had acute miliary tuberculosis[4]. None of these patients had received streptomycin prior to this time. Only one received concomitant PAS. All received intrathecal medication.

Three of the surviving patients are well without sequelae; the fourth is deaf, severely ataxic with disabling vertigo and tinnitus. Two of these patients were considered on clinical grounds, admittedly tenuous, to have possibly a delayed adult primary progressive tuberculosis with meningitis although this was not confirmed by a known conversion of the cutaneous reaction to tuberculin. The survival of these four patients seemed completely fortuitous since two of them at times during the course of their disease appeared comatose and moribund.

Although 11 patients (22 per cent) survived less than one week following the institution of chemotherapy, streptomycin therapy proved effective in prolonging the duration of the illness in the series as a whole. The mean survival time was approximately eight weeks from the onset of therapy. One patient's illness was prolonged to eighty-four weeks. The mean duration of the disease was approximately twelve weeks for Negroes, compared with six weeks for the white patients. The significance of this difference is not clear but may be related to a

[4] The term *miliary tuberculosis of the lung* is used to describe an acute or chronic hematogenous tuberculous dissemination throughout the pulmonary circulation. By exact definition, the descriptive adjective *miliary* refers only to the size of these lesions but usage condones a pathogenetic implication.

more acute fulminating type of hematogenous dissemination seen not infrequently in white patients. No correlation was noted between survival times and the various therapeutic regimens with the exception of those patients who received supplementary PAS.

PAS appeared to have no effect upon mortality. Three of the 4 surviving patients did not receive PAS. The mean survival time of the patients who did receive PAS, however, was approximately eighteen weeks compared with an approximate survival time of six weeks for the group of patients who were not treated with this drug. It should be remembered, however, that the most seriously ill patients with the shortest hospital courses were often unable to tolerate oral medication. The use of concomitant PAS did not prevent the development of meningitis in 3 of the 14 patients who developed meningitis while on intramuscular medication.

DISCUSSION

The first of the various factors responsible for these strikingly poor therapeutic results is the frequent association of tuberculous meningitis in the adult with actively disseminating widespread hematogenous extrapulmonary tuberculosis. This association is thought by Auerbach (22) to represent important pathogenetic and prognostic differences between the disease as it appears in adults and children, in whom the meningitis usually is part of the pattern of a progressive primary dissemination. In the present series, widespread extrapulmonary tuberculosis was invariably a common finding, both clinically and at necropsy.

It is of interest that intracranial tuberculomas were demonstrated in only 4 of the autopsied cases, but the frequent difficulty in demonstrating these possible foci of dissemination to the meninges on routine examinations is well known. In an additional 2 patients the presence of intracranial tuberculoma was diagnosed following exploratory craniotomies, and in 5 other patients tuberculomas were suspected clinically because of localizing neurologic and electroencephalographic findings.

Choroidal tubercles were seen in only 4 patients, all with complicating miliary tuberculosis. This represents a surprisingly low incidence of choroidal tubercles compared with the incidence of 60 per cent in a series reported by Illingworth and Wright (23).

No datable clinical manifestations of hematogenous tuberculosis except meningitis could be elicited in one group of 12 patients. In a second group of 11 cases, miliary tuberculosis and tuberculous meningitis diagnosed simultaneously were the only manifestations of hematogenous dissemination. In the remaining 37 patients, however, meningitis was the terminal clinical manifestation of progressive hematogenous tuberculosis, which in one patient began twenty-five years before meningitis developed (table 2).

No precipitating factor to explain the onset of meningitis could be determined in the majority of cases except in one small group of 7 patients (12 per cent), in whom meningitis developed shortly after some operative procedure for extrapulmonary tuberculosis. In 3 of the 7 cases, the operative procedure had been

TABLE 2

TIMETABLE OF PROGRESSIVE HEMATOGENOUS TUBERCULOSIS TERMINATING IN MENINGITIS

PATIENT	NODES	PLEURISY	PERITONITIS	SPINE	SKIN	KIDNEY	BRAIN	MILIARY	MENINGITIS
J. A.								December 1950	March 1951
L. A.								October 1946	December 1946
B. B.							May 1946		June 1949
MSB.								January 1948	May 1948
A. C.								September 1949	December 1949
M. C.		1940	January 1948						June 1948
T. C.					1933	March 1947			April 1947
K. C.				October 1948				July 1948	August 1948
H. C.								September 1948	January 1949
M. D.	1941		August 1947						October 1947
B. E.					September 1946				December 1946
J. F.		August 1945							October 1946
V. G.	November 1949							April 1950	April 1950
D. H.		April 1949							April 1950
W. H.				1935					July 1947
J. M.	August 1950								January 1951
P. McG.				December 1947					May 1948
R. McN		1938						January 1951	January 1951
J. McN								June 1948	November 1948
F. M.	1945						May 1948		June 1948
L. M.		May 1947							December 1951
E. N.	December 1947	February 1948							July 1948
D. N.	October 1947								December 1947
*H. N.					May 1949			June 1948	June 1948
O. O.		January 1947							January 1947
J. P.			October 1946						May 1947
A. P.								June 1948	October 1948
H. P.								March 1950	May 1950
Dol. P.				December 1950				November 1948	December 1950
R. P.		April 1945		March 1949				March 1949	August 1949
F. P.	1923								August 1948
R. R.		1939						November 1948	December 1948
L. R.				December 1945				November 1946	January 1947
J. R.		June 1949						June 1949	August 1949
J. T.	September 1943	January 1944		February 1947					November 1948
H. W.	June 1948			September 1949				February 1950	June 1950
*R. W.	December 1948	May 1948							February 1947

* Both of these patients later had fatal relapses of their meningitis. H. N. died in September, 1949, and R. W. died in November, 1948.

accompanied by chemotherapy. The procedure consisted of a spinal fusion in 2 instances. Other operative procedures which were followed at an interval of one week to forty-seven days (average, three weeks) by the appearance of meningitis were nephrectomy for a tuberculous kidney; incision and drainage or excision of tuberculous cervical nodes; exploratory craniotomy for tuberculoma; and excision of a supraclavicular cold abscess. Although difficult to prove, it appears that this sequence of events was not coincidental. Meningitis in one patient developed less than four weeks after a normal full-term spontaneous delivery.

A possibly artificial distinction has been created (at least in adults) between cases of tuberculous meningitis with and without roentgenographically demonstrable evidence of acute miliary involvement of the lungs. Twenty-nine patients (48 per cent) had accompanying miliary tuberculosis, demonstrated roentgenographically. This incidence is considerably higher than the reported incidence of miliary tuberculosis complicating childhood tuberculous meningitis (8, 9, 12, 24) and is also a higher incidence when compared with other adult series (3, 11). The highest incidence of this complication (58.5 per cent) has been reported by Illingworth and Lorber (3), but the actual incidence in all series is undoubtedly higher than reported since the absence of roentgenographic evidence does not exclude miliary tuberculosis if the lungs are examined at necropsy (25). Among this group of 29 cases, the diagnosis of miliary tuberculosis and tuberculous meningitis was made simultaneously in 14 patients. In 15 patients, however, meningitis followed the miliary disease by a mean time of approximately fourteen weeks. In one instance, twenty-five months elapsed following the onset of an acute miliary pulmonary seeding which responded well to streptomycin therapy before a terminal tuberculous meningitis occurred. There were no cases of the development of an acute pulmonary hematogenous dissemination following the meningitis.

One reason for drawing a distinction between cases of tuberculous meningitis following or accompanying miliary tuberculosis and cases of meningitis in which miliary disease of the lungs is absent is the finding in several large series that the prognosis of tuberculous meningitis is worse if miliary tuberculosis is present (5, 7, 11, 14, 26–28). The miliary tuberculosis in this series responded well to chemotherapy. Four of the patients have been included in a recent article by Cournand and his associates (29) describing the often rapid and dramatic functional, roentgenographic, and morphologic improvement which follows adequate antimicrobial therapy. The results in this series do not support the premise of a poorer prognosis if miliary disease is present and are in agreement with another report (3) that there is no significant difference in the survival rate of patients with meningitis with and without clinical evidence of miliary tuberculosis. One of the 4 survivors in the present series had roentgenographically demonstrable miliary disease.

The mean duration of meningitis for patients with miliary disease was ten weeks (average, sixteen weeks) compared with a mean of twelve weeks (average, fifteen weeks) for patients without this complication. The clinical course followed by the members of the two groups is presented in table 3. After one week of

therapy, 27 per cent of the patients with miliary disease were dead, compared with 12 per cent of patients without miliary tuberculosis. After one month of therapy, 31 per cent of both groups were dead. The death rate for the miliary group was then slightly higher until the end of the fourth month, when 56 per cent of both groups had died. During the next few months the death rate was slightly higher for the nonmiliary group until the end of the ninth month of therapy, at which time 86 per cent of both groups had died. The longest survival

TABLE 3

SURVIVAL TIME FOLLOWING INITIATION OF THERAPY IN PATIENTS WHO DIED WITH TUBERCULOUS MENINGITIS WITH AND WITHOUT MILIARY TUBERCULOSIS

	(27) WITH MILIARY	PER CENT	(26) WITHOUT MILIARY	PER CENT	TOTAL	TOTAL PER CENT
1 week or less	7	27	4	12	11	22
1 week to 1 month	1	31	5	31	6	33
1 to 2 months	4	46	1	35	5	42
2 to 3 months	2	52	2	43	4	50
3 to 4 months	1	56	6	56	7	64
4 to 5 months	3	68	3	78	6	75
5 to 6 months	1	72		82	1	77
6 to 7 months	1	76	1	82	2	80
7 to 8 months	2	82			2	83
8 to 9 months	1	86	1	86	2	86
9 to 10 months	2	92	2	95	4	94
10 to 11 months						
11 to 12 months	1	96			1	96
12 to 13 months						
13 to 14 months						
14 to 15 months	1	100			1	98
15 to 16 months						
16 to 17 months						
17 to 18 months						
18 to 19 months						
19 to 20 months						
20 to 21 months			1	100	1	100
Totals	27		26		53	

period for a fatal case of tuberculous meningitis with preceding miliary disease was fifteen months, compared with twenty-one months for one patient without miliary tuberculosis.

Except for the cases of tuberculous meningitis in children with miliary disease and extensive hematogenous dissemination, the seeds of tuberculous meningitis are probably sown in different ground in the adult than in the child. Auerbach's explanation of the more favorable prognosis of the disease in children is a plausible one. In the child with a postprimary meningeal infection, the source of dissemination to the meninges may be eliminated by healing of the primary infection. In the adult the meningitis may be secondary to many foci of active extra-

pulmonary tuberculosis which possibly give rise to hematogenous metastases with repeated reinfections of the meninges. These episodes of reinfection may be related to clinical relapse, which was another factor contributing to the poor therapeutic results in this series.

Presumably as a consequence of premature cessation of therapy, 17 patients (28 per cent) developed a total of 20 clinical and bacteriologic relapses, 16 of which terminated fatally. Relapse usually developed within a few weeks to a few months following termination of therapy, although one patient survived in apparent good health for fifteen months before relapse occurred. The cerebrospinal fluid findings in these patients were all markedly abnormal at the time therapy was discontinued. Intrathecal streptomycin may cause a pleocytosis and an elevation of the protein content of the cerebrospinal fluid (9, 10). Hence, the most significant abnormality on cessation of therapy was a low cerebrospinal fluid sugar concentration in 11 of the 14 patients whose cerebrospinal fluid findings were available. Because of this experience and also because of the experience of others (1–3, 5, 8, 12, 27, 28, 30), therapy is now continued for a longer period. The present practice in this clinic is as follows: parenteral streptomycin is given, 1 gm. twice daily, for at least six months or longer; intrathecal streptomycin, 50 mg. daily, is administered for four weeks, then three times each week for the balance of a six-month treatment period unless the cerebrospinal fluid is normal before that time. Variations from this therapeutic program are inevitable owing to the many clinical variables which may be encountered in any one given case.[6]

Another factor contributing to the poor therapeutic results in the present series may have been the emergence of drug-resistant tubercle bacilli. This phenomenon may have resulted, not only from prolonged treatment of the meningitis itself, but during prolonged antimicrobial therapy for hematogenous tuberculosis or pulmonary tuberculosis prior to the onset of meningitis. Twenty-five patients (43 per cent), only 5 of whom received concomitant PAS, received streptomycin or dihydrostreptomycin before meningitis developed. Several received total amounts of streptomycin which varied between 200 and 300 gm. There is some evidence that drug-resistant tubercle bacilli do not emerge to predominance so rapidly in the treatment of meningitis as in pulmonary and other types of extra-meningeal tuberculosis (7, 14, 27, 30, 31). Nevertheless, drug neutralization as a consequence of the emergence of drug-resistant bacilli may have been a factor which would explain the poor results in the present series.

Many investigators, particularly those who have reported series of tuberculous meningitis in children, have stressed the prognostic importance of early diagnosis and prompt institution of therapy (3, 5, 7, 9, 10, 12, 27, 31–33). Delay in instituting therapy could explain the poor results in 11 patients of the present series who were admitted in the terminal stages of the disease and who survived only a few days. In 37 (62 per cent) of the patients, however, clinical symptoms had been present for only two weeks or less before chemotherapy was instituted.

[6] Since this article was submitted for publication, a new chemotherapeutic regimen for tuberculous meningitis has been instituted which consists of the substitution of isoniazid for intrathecal streptomycin.

Three of the 4 known survivors were started on treatment within the second week of symptoms, and the fourth by the third week. The desirability of early treatment is obvious but from this study would not appear to have the prognostic significance that it has in children. Of 9 patients who had had symptoms for less than one week, all died.

There is undoubtedly a clinically silent phase in the natural history of tuberculous meningitis during which the meningeal infection is active and progressive and can be diagnosed only by routine lumbar puncture. By the time the characteristic clinical and cerebrospinal fluid changes occur (particularly overt signs of meningeal irritation, a low cerebrospinal fluid sugar, and dissemination of sufficient tubercle bacilli throughout the cerebrospinal fluid to enable their demonstration on direct smear), in many instances the meningitis is probably no longer in the early reversible stage. The clinical and cerebrospinal fluid findings upon which an unequivocal diagnosis of tuberculous meningitis can be made are probably late manifestations in terms of reversible pathology. As the patient is being committed to many months of an extremely traumatic and arduous regimen of therapy, the appearance of these criteria are sometimes awaited before treatment is begun. It is difficult to decide whether to begin treatment on presumptive or inconclusive evidence or whether to delay initiating therapy in fear of either masking the clinical picture or treating some nontuberculous condition as a tuberculous meningitis. In order to demonstrate the preclinical manifestations of a tuberculous meningeal involvement, routine lumbar punctures should frequently be carried out on patients under treatment for miliary tuberculosis or on those in whom actively disseminating tuberculosis is suspected. It has been estimated that 50 to 67 per cent of adults with miliary tuberculosis will at some time develop meningitis (31).

Possibly the most important factor to explain treatment failure is the nature of the pathologic process which occurs at the base of the brain, which is complicated, paradoxically enough, by the stimulus to healing offered by prolonged chemotherapy which continues for many months. These pathologic changes, the direct result of the protracted course which treated tuberculous meningitis now follows, have been discussed in three recent reports and the autopsy findings in the present series were quite similar to those described in these papers. Auerbach (22) has noted that in treated cases there is a degree of caseation far in excess of that found in the untreated cases and a marked proliferation of granulation tissue which, as the process of healing continues, is replaced by hyalinized connective tissue. Similar findings are reported by Levinson and his coworkers (34), who found little evidence that the initial exudate is ever absorbed but that healing occurs by hyalinization or fibrous walling off of a still caseous focus, a nidus for possible later dissemination. The reparative processes induced by streptomycin have been described (35) as follows:

> Streptomycin induces a definitive reparative process in tuberculous meningitis as shown by the prolongation of life and the pathological changes observed in these fatal cases. These apparently occur as follows:
>
> The exudate in the subarachnoid space undergoes progressive organization. There is early dissolution of much of the fibrin and replacement by actively pro-

> liferating fibroblasts and chronic inflammatory cells. The foci of necrosis tend to be either encapsulated or partially infiltrated by fibroblasts. The acute tuberculous arteritis, commonly involving the vessels in the Circle of Willis and proximal branches of the middle cerebral arteries, rapidly is transferred into a proliferative endarterial reaction causing severe stenosis or occlusion of vessels. Multiple ischemic softenings which are consistent in the basal ganglia and internal capsule result from the endarteritis and are a common cause of neurological sequelae. . . . The outstanding complications of streptomycin-treated tuberculous meningitis are communicating hydrocephalus and multiple ischemic softenings of the brain.

These reparative processes secondary to chemotherapy present problems quite analogous to those seen in the long-term combined chemotherapy of pulmonary tuberculosis or of tuberculosis of any organ. They are not, however, because of obvious anatomical reasons, amenable to collapse or excisional surgery. That the meningitis can occasionally resolve following the use of streptomycin is demonstrated in sections obtained from autopsied material on 2 patients who died from nonmeningitic causes. The more usual course, however, is the development of a fibrin rich caseous exudate, which sometimes extends into the brain with an accompanying meningoencephalitis, in which adequate concentrations of antituberculous drugs probably cannot be maintained. The difficulty in preventing the serious consequence of cerebral ischemia and infarcts is shown by the often extreme degree of intimal proliferation frequently noted in our autopsy material.

Our thinking in terms of the chemotherapy of tuberculous meningitis should constantly be molded and directed by concepts derived from the pathologic processes and the implications involved. Let it be assumed that drug-susceptible tubercle bacilli are present and that the extent of extra-meningeal tuberculosis does not make the prognosis hopeless even without a supervening meningitis. The problem then consists of how to get high concentrations of drug into contact with the tubercle bacilli while the meningitis is still in the early reversible stages, while at the same time preventing the organization and fibroblastic proliferations of the fibrinous tuberculous exudate. Since the prevention of irreversible organization of the basal tuberculous exudate would undoubtedly contribute to a materially better prognosis, further early use of the lytic enzymes, streptodornase and streptokinase, should be investigated. One group of investigators has reported no significantly better results following the intrathecal use of these substances (35). The encouraging results of another group (37), however, particularly when the enzymes are given from the very onset of therapy before organization of the inflammatory reaction has begun, deserve further investigation. With the hope of retarding this fibrous organization, it has recently been suggested (38) that the hormones, corticotropin and cortisone, should have a place in the routine clinical management of tuberculous meningitis. In at least one instance (39), success has been reported following the administration of cortisone in the resolution of a lumbar subarachnoid block which had not been achieved through the prior administration of streptokinase and streptodornase.

It is possible that, from the beginning, streptomycin should be administered either intracisternally or intraventricularly, either with or without concomitant intrathecal therapy, in an attempt to bring high concentrations of drug into close contact with the meningeal inflammation. Perhaps therapy should be

begun solely on the basis of a pleocytosis, collodial gold curve changes, and a rise in cerebrospinal fluid streptomycin concentrations without waiting for other confirmatory evidence of an active meningitis to develop. Flori (1), who reported two hundred and sixty-five bacteriologically proved cases of tuberculous meningitis, found that the fluid obtained from cisternal puncture gave a higher incidence of positive findings than fluid obtained from routine lumbar puncture. It is possible, therefore, that this procedure should be done routinely in the hope of making an earlier bacteriologic diagnosis. Further use of intrathecal tuberculin, as suggested by the group of Oxford workers, should be explored (26).

That progress has been made in the treatment of this disease cannot be denied. The adjustment of dosage regimens and the introduction of newer antimicrobial drugs is not the entire answer and may receive undue emphasis which fails to represent realistic thinking. Further progress is doubtful unless it be agreed that early heroic therapy (preferably in the asymptomatic stage of the disease) by the internist, neurologist, and neurosurgeon working as a team, in an attempt to prevent, rather than treat, the irreversible phases of tuberculous meningitis is the only rational course to follow.

SUMMARY

The results of the treatment of 60 consecutive cases of tuberculous meningitis in adults on the Bellevue Hospital Chest Service with various regimens of chemotherapy are presented. There were 53 known deaths (89 per cent) and 4 known survivors (6 per cent). The responsible factors are discussed in some detail and suggestions are offered of ways to perhaps improve these discouraging therapeutic results.

SUMARIO

La Meningitis Tuberculosa en el Adulto: Repaso de Sesenta Casos Consecutivos Tratados con Estreptomicina

Preséntanse los resultados del tratamiento de 60 casos consecutivos de meningitis tuberculosa en personas adultas asistidas en el Servicio Torácico del Hospital Bellevue con varios regímenes quimioterapéuticos. Hubo 53 muertes conocidas (89 por ciento) y 4 sobrevivencias conocidas (6 por ciento). Discútense algo a fondo los factores causantes y ofrécense indicaciones relativas a modos de mejorar quizás esos desalentadores resultados terapéuticos.

RESUME

La méningite tuberculeuse chez l'adulte: Analyse des observations d'une série de soixante cas traités par la streptomycine

Présentation des résultats obtenus chez l'adulte dans une série consécutive de soixante cas de méningite tuberculeuse soumis à différents régimes du traitement antibiotique, dans le service des maladies du pouvon au Bellevue Hospital (New York City). Il y a eu 53 décès connus (89%) et 4 survivants connus (6%). Les facteurs responsables sont l'objet d'une étude assez détaillée et certains moyens susceptibles d'améliorer ces résultats thérapeutiques décourageants sont proposés.

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A TOXIC LIPID COMPONENT OF THE TUBERCLE BACILLUS ("CORD FACTOR")[1]

I. Isolation from Petroleum Ether Extracts of Young Bacterial Cultures

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INTRODUCTION

In a paper recently published in this journal, Philpot and Wells (1) reported that they were unable to confirm some earlier experiments by the present writers which described the isolation and some biologic properties of a lipid extract from young cultures of virulent tubercle bacilli. The discrepancy between the results of Philpot and Wells and those of the present writers made it seem advisable at this stage to make a report on the progress of the work in this laboratory.

The lipid material in question had been termed "cord factor" because it was obtained from "cord-forming" strains of *Mycobacteria* (virulent tubercle bacilli and BCG). As first described (2), it was a crude petroleum ether extract from young, living, surface-grown cultures which had two characteristic biologic properties. It inhibited the migration of leukocytes *in vitro* and exerted a delayed toxicity for mice which would become manifest after repeated intraperitoneal injections of relatively small doses. The latter activity seemed to lend itself to assaying the material biologically, especially for quantitative determinations during the process of chemical purification, because no other constituents of the tubercle bacillus are known to have a similar toxic action. This is in contrast to the inhibitory action on the migration of leukocytes which can be exerted by various bacterial products (3, 3*a*–3*c*). As a consequence, the latter technique is of questionable value in tracing the toxic material during chemical fractionation.

It was recently reported that the crude petroleum ether extract which shows the characteristic toxicity for mice consists of a mixture of several compounds (4). These fractions are different biologically, and only a small proportion, representing approximately 1 per cent of the total extract, is toxic. It will be shown in the present report that this part can again be separated into a toxic and nontoxic moiety.

With the small amounts available for study at the present time, the toxic fraction could be concentrated, but could not be obtained in pure form. The concentrated toxic product is less than one-hundredth of the original crude material, i.e., less than one ten-thousandth of the bacterial cultures which were first extracted with petroleum ether. In these circumstances, it is evident that

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the scarcity of the material available for experimentation was the greatest handicap throughout this work. It has not been possible thus far to accumulate enough of a uniform stock to repeat animal experiments for a longer period of time with the same batch of material. Consequently, a reliable, reproducible method for assaying various extracts had to be found which permitted the standardization of new material. Because of its high sensitivity, the toxicity for mice proved to be the best test.

The present report is concerned with the chemical purification and the biologic assay of "cord factor." The extraction of similar material from sources other than young cultures of virulent bacteria and their chemical and biologic properties will be described in succeeding reports (5, 6).

EXPERIMENTAL

The Extraction of "Cord Factor" from Young Cultures

The method for the extraction of "cord factor," previously described in detail (2), was not significantly changed in the present studies.

The bacteria are harvested approximately one week after the cultures begin to spread across the surface of the nutrient medium, i.e., usually two weeks after inoculation. At this stage, the bacterial veils are still thin and barely cover the surface. Occasionally, they creep up along the glass walls of the flasks but they do not form thicker masses. The cultures are filtered through paper (Whatman No. 5) on a Buchner funnel and washed with water. Instead of extracting the bacteria in a beaker under mechanical stirring, as was originally done, it was found to be more convenient to transfer them to a new Buchner funnel and extract by washing repeatedly with petroleum ether on the filter. The filtrates are centrifuged and passed through bacterial filters in the same way as was previously described. After evaporation of approximately 80 per cent of the solvent, the concentrated extracts are precipitated from alcohol and the dried precipitates used as starting material for purification. Usually, the yields from several culture batches are collected and the pooled crude extracts are used for chemical work.[1]

The Biologic Assay of "Cord Factor"

The test consists of determining the minimum amounts of material which upon two to four intraperitoneal injections cause the death of mice of the C57 Black strain. The animals die within one to two weeks after the first injection. At autopsy, they show extended hemorrhages of the lungs. This is a constant and typical finding which makes the test a useful and sensitive tool for assaying various chemical fractions of the tubercle bacillus. A detailed description of the test and of the histopathologic findings in the mice has recently been published (7).

[1] All material referred to in this paper was obtained from surface cultures of the H37Rv human strain of *M. tuberculosis* except for a few duplicate experiments in which the bovine strain Vallée was used. At one time, the H37Rv cultures spread slower and slower and became quite clumpy instead of forming fine veils. Likewise, the petroleum ether extracts lost their toxicity to a considerable degree. New surface cultures were then started from solid Löwenstein medium in which the strain had also been propagated regularly. This restored the original growth characteristics of the cultures as well as the toxicity of the material extracted from them.

Specificity of the Biologic Assay

For practical purposes, this test has proved satisfactory. It is reproducible and gives quantitative results. Mice respond essentially with three types of reactions to injections of various bacterial fractions:

No visible reactions

An acute toxic reaction in the course of which mice die within a few days without showing characteristic symptoms at autopsy

A delayed type of toxic reaction in the course of which mice die within one to two weeks with considerable loss of weight and characteristic extensive pulmonary hemorrhages

The three types can easily be distinguished from one another.

In view of Philpot and Wells' (1) failure to observe any kind of reaction in mice after injecting the animals with bacterial lipids, the possibility was again investigated whether the response which had been considered typical was char-

TABLE 1

SUSCEPTIBILITY OF VARIOUS STRAINS OF MICE TO INJECTIONS OF TOXIC MATERIAL FROM CULTURES OF H37Rv AND TO INFECTION WITH TUBERCLE BACILLI H37Rv

STRAIN OF MICE	SUSCEPTIBILITY TO INJECTION				SUSCEPTIBILITY TO INFECTION			
	Number of Mice	Number of Injections	Dose per Injection	Number of Deaths with Typical Symptoms	Number of Mice Dying	Average Survival Time	Range	Number of Mice Sacrificed After 40 Days
						days	*days*	
dba 1	10	3	0.01 mg.	9	10 of 10	18.8	17–22	0
C57 Black	10	2	0.01 mg.	8	9 of 10	18.8	15–22	1
dba 2	10	4	0.01 mg.	8	9 of 10	20.9	20–25	1
C57 Brown	10	2	0.01 mg.	8	10 of 10	22.2	17–33	0
C3H	10	4	0.01 mg.	4	10 of 10	24.9	22–26	0
B alb. C	10	4	0.01 mg.	2	10 of 10	27.4	21–39	0
CF 1	10	4	0.01 mg.	1	10 of 10	24.5	19–34	0

acteristic of one particular strain of mice. It was possible that the toxicity of a given material would not be detected if nonsusceptible animals were used. In the initial report on this subject, it was mentioned that different strains of mice appeared to have a different degree of susceptibility to the toxic action of "cord factor" and that the susceptibility to this toxic action seemed to be parallel to the susceptibility of these mice to tuberculous infection (2).

In table 1 may be seen the results of a typical experiment in which groups of various strains of mice were tested for susceptibility both to "cord factor" injections and to infection with virulent tubercle bacilli (H37Rv). The following strains of mice were compared: dba line 1, dba line 2, C57 Brown, C57 Black, C3H, B albino C, and CF I. The last-named strain was received from Carworth Farms, New City, New York; all of the other mice came from the Jackson Memorial Laboratories, Bar Harbor, Maine.

The results of this experiment confirm the earlier finding that there are marked differences between various strains of mice. Likewise, a certain parallel

was again found between susceptibility to the toxic action of "cord factor" and the effects of infection. The only exception to this rule was the CF I strain, which had a high susceptibility to infection and at the same time was relatively resistant to the toxicity of the bacterial extract. It should be emphasized, though, that in the present experiment the amounts of "cord factor" injected were kept small (4 times 10 γ) in order to detect finer distinctions. CF I mice are susceptible and die from injections of larger doses. Comparable differences in the susceptibility of mice to tuberculous infection were described by Pierce, Dubos, and Middlebrook (8).

The Chemical Purification of the Toxic Component of Crude Petroleum-Ether Extracts from Virulent Tubercle Bacilli

The toxic principle was separated according to the accompanying scheme.

The crude petroleum ether-extracted material was a colorless powder, melting point 30° to 34° C. Stained according to the Ziehl-Neelsen technique, it was alcohol-acid fast. The neutral red test of Dubos and Middlebrook (9) was weakly positive after thirty minutes. This is in contrast to the strong positive reaction given by lipopolysaccharides (10). Microtitration showed a low degree of acidity.[3] With the crude material, Fehling's test was negative but became positive after acid hydrolysis.

The following ignition values were found:

3.317 mg. material gave 9.77 mg. CO_2 and 3.63 mg. H_2O
3.810 mg. material gave 11.19 mg. CO_2 and 4.49 mg. H_2O
4.556 mg. material used 0.85 ml. 0.02-n $Na_2S_2O_3$ solution (f = 0.1034)
6.702 mg. material used 1.09 ml. 0.02-n $Na_2S_2O_3$ solution

found:	C	H	OCH_3
	80.39%	12.92%	1.93%
	80.13%	13.18%	1.68%

The crude "cord factor" preparations gave negative reactions for phosphorus (12, 12*a*) (less than 0.1 per cent P, if any). Phosphorus-containing lipopolysaccharides from tubercle bacilli and lecithin served as controls in these tests. Equally negative were the reactions for nitrogen (lime test; Lassaigne's test; less than 0.4 per cent N, if any).

After precipitating the crude extracts from ether solutions into ethanol, the precipitates were extracted in small volumes of boiling acetone. A typical example is described below.

Extraction with acetone: Seven hundred and five milligrams of crude material obtained as a precipitate from alcohol were heated fifteen times in 5 ml. of acetone, each just to the boiling point. After each operation the warm supernatant was decanted. A colorless precipitate (A) separated in the cold from the acetone extracts. All extracts were then concentrated *in vacuo* and the residua re-extracted with acetone in the same way. The pooled hot acetone-insoluble parts weighed 23 mg (B). Biologic tests showed toxicity in B, whereas A was nontoxic.

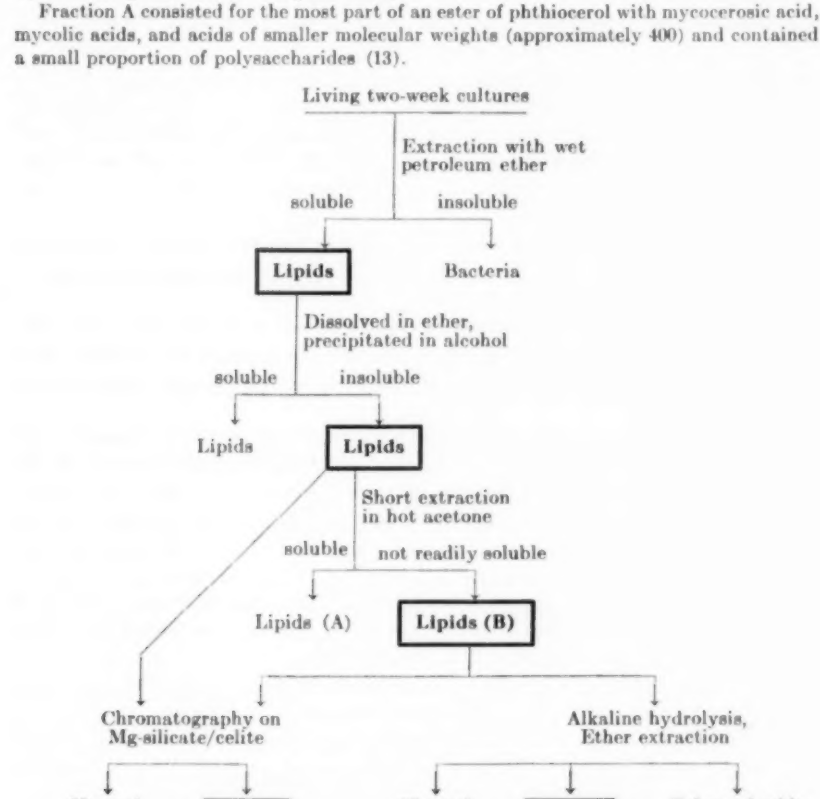
Fraction B was soluble in petroleum ether, ether, benzene, and chloroform; it was insoluble in methanol, ethanol, and water. After boiling B in larger amounts of acetone for at least thirty minutes, most of it was dissolved. The activity resided in the soluble part.[4]

[3] The microtitration of a pool of several batches of crude material gave a value of 0.00122 ml. of 0.1-n KOH per mg. of material. Calculated on a molecular weight of approximately 1,200, this corresponds to a content of approximately 1 per cent of mycolic acid type of compound. It is interesting to note in this connection that, according to Asselineau and Lederer (11, 11*a*), free mycolic acid is found only in virulent strains of tubercle bacilli.

[4] The solubility of the active material in acetone depends partly on the properties of the inactive material present in the same sample (*see also* (5)).

Fraction B was acid fast. It showed negative tests for phosphorus (less than 0.05 per cent P) and nitrogen (less than 0.09 per cent N).

Fraction A consisted for the most part of an ester of phthiocerol with mycocerosic acid, mycolic acids, and acids of smaller molecular weights (approximately 400) and contained a small proportion of polysaccharides (13).



Hydrolysis of fraction B: The active portion B was then subjected to alkaline hydrolysis. This procedure yielded three different fractions:

1. Ether-soluble potassium salts and neutral components (Bn)
2. Ether-insoluble potassium salts of acids (Bs)
3. The remaining aqueous phase containing traces of carbohydrates partly liberated during hydrolysis (Bw)

In a typical experiment, the hydrolysis was performed as follows: 18 mg. of fraction B were dissolved in 0.5 ml. of benzene and 0.1 ml. of 5 per cent methanolic potassium hydroxide and heated in a boiling water bath for six hours. Traces of polysaccharides precipitated during the process. This is in contrast to the behavior of lipopolysaccharides which yield up to 50 per cent of polysaccharides during this treatment (11). After evaporation *in vacuo*, the residue was treated with water and repeatedly extracted with ether. The ether extract was washed with 2-N hydrochloric acid and water and dried over sodium sulfate. After evaporation of the ether, 12 mg. of dry residue were left, i.e., the fraction Bn.

The alkaline aqueous extract was acidified and extracted with ether-chloroform, washed, dried, and the solvents evaporated. Three and one-tenth milligrams of residue were left, i.e., the fraction Bs.

The aqueous parts obtained from alkaline extraction of the ether were neutralized with sodium bicarbonate and the water was evaporated *in vacuo* (Bw). Fehling's test was negative with this sample, but became strongly positive after acid hydrolysis.

Neither the Bn nor the Bw fractions showed toxicity. The characteristic activity was present only in fraction Bs. While the amounts yielded in the various fractions varied slightly from one experiment to another, the biologic activity of the three fractions remained the same from batch to batch. It was thus possible to trace the toxic properties to one fraction of the material, but the biologic activity did not increase according to the chemical concentration. This suggested that the active material was partly inactivated or destroyed during the process of hydrolysis, which made it necessary to search for milder chemical methods of concentration and purification.

Fractionation of B and Bs by chromatographic methods: Attempts were made to further fractionate B and Bs by chromatography, using neutral aluminum oxide activated at 180° C. as the adsorbing agent (14). The biologic activity was found in the portions eluted with ether-acetic acid, but it still was not possible to concentrate the activity proportionally to the weight of the fractions in which activity was found. The loss was attributed to the high adsorbing quality of aluminum oxide. It was then found that magnesium silicate-celite was a more satisfactory adsorbent. This material was prepared as follows:

> Two parts per weight magnesium silicate and one part per weight "Johns Manville" Celite #545 were suspended in water, acidified under constant stirring with glacial acetic acid, and the supernatant decanted. The mixture was then shaken with hot water and the supernatant discarded, an operation repeated until the supernatant was neutral. The water was removed by filtration, the material washed three times with methanol and ether, and dried *in vacuo*. Finally, it was activated by heating to 150° C. *in vacuo*[5] for thirty minutes, after which operation it was ready for use.

[5] New experiments showed that the adsorbent activated without application of vacuum has equally good separating qualities.

An example of a chromatography of active material is presented in table 2. For this chromatography, 75 mg. of fraction B were dissolved in 7.5 ml. of petroleum ether and filtered through 2.5 gm. of magnesium silicate-celite. For each elution, 7.5 ml. of solvent were used. Approximately 100 per cent of the material was recovered. In this experiment, only fraction B, which is slightly soluble in acetone, was passed through the column, but the same procedure was

TABLE 2

CHROMATOGRAPHIC SEPARATION OF FRACTION B. (Chromatography I)

FRACTION	ELUTED WITH 7.5 ML. OF:	YIELD	TOXICITY TEST			
			Amount Injected per Dose*	Number of Injections	Number of Mice Dying with Typical* Symptom	Degree of Toxicity†
		mg.	mg.			
1	Petroleum ether	0.0				
2–4	Petroleum ether	traces	0.1	5	0 of 5	0
5	Petroleum ether/benzene 1:1	36.5				
6	Petroleum ether/benzene 1:1	21.5	0.1	5	0 of 5	0
7	Petroleum ether/benzene 1:1	2.5	0.1	5	0 of 5	0
8	Petroleum ether/benzene 1:1	1.0	0.1	5	0 of 5	0
9	Petroleum ether/benzene 1:1	1.6				
10	Benzene	0.7	0.1	5	0 of 5	0
11	Benzene	2.0				
12	Benzene/ether 1:1	5.5				
13	Benzene/ether 1:1	0.3	0.1	5	0 of 5	0
14	Ether	trace				
15	Ether	0.0				
16	Ether/acetic acid 5%	0.0	0.1	3	5 of 5	
17	Ether/acetic acid 5%	trace	0.05	3	5 of 5	
18	Ether/acetic acid 10%	1.2	0.025	3	5 of 5	+++
19	Ether/acetic acid 10%	2.1	0.012	4	5 of 5	
20–21	Ether/acetic acid 10%	traces	0.006	5	0 of 5	
22	Ether/acetic acid 10%	0.0				

* The number of dilutions tested as well as the number of mice in each group was limited by the amount of material available of each fraction.

† Arbitrary rating for easier reading of the results.

The brackets in this table indicate how some of the fractions were pooled for biologic testing.

later successfully employed with the entire crude material precipitated from ether.

For the biological assay, fractions 1 to 4, 13 to 15, and 16 to 22 were pooled and the remaining fractions were tested individually. As may be seen from table 2, the toxicity appeared in the portions eluted with ether-acetic acid (fractions 16 to 22). Of a pool of these fractions, three injections of 12 γ each were lethal for mice; whereas three injections of 6 γ each caused severe loss of weight and death to one of 5 mice (table 2). This represents a ten- to twenty-fold concen-

tration of the active principle as the crude material did not show toxicity when less than 4 × 0.1 mg. were injected.

The following data concerning some of the chromatography fractions are of interest:

Fractions 5 and 6: Melting point, 28° to 33° C. These fractions consisted chiefly of an ester of phthiocerol with mycocerosic acid (13).

Fractions 16 to 22 (active fractions): Melting point, 36° to 41° C. Characteristic ultraviolet absorption spectrum, λ max. 213 mμ (log. ε = 2.85) in ether, calculated for an equivalent molecular weight of 1,200 (c = 2.60×10^{-3} mol. per liter). Some acidity was revealed by the hydroxamate method (15). Microtitrations (11) suggested an equivalent molecular weight of 1,560 plus or minus 10 per cent. The material which was still not chemically pure was acid-alcohol fast.

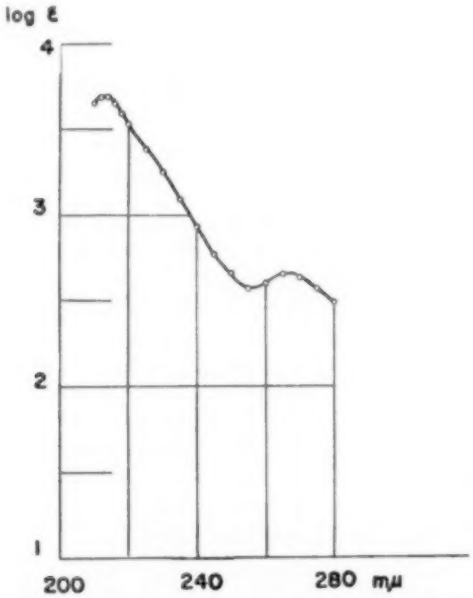


FIG. 1. Ultraviolet absorption spectrum of a concentrated toxic fraction in ether solution ("Unicam" spectrophotometer S.P. 500).

Rechromatography of the material eluted with ether-acetic acid: Twenty milligrams of toxic material eluted with ether-acetic acid were dissolved in 2.0 ml. of petroleum ether and filtered through 0.5 gm. of magnesium silicate-celite. Two milliliters of each solvent were used for elution. Nineteen and five-tenths milligrams were recuperated.

The details of this chromatography and the results of the biologic tests are

shown in table 3. The most active fractions, 28 to 31, which were re-precipitated from ether with methanol had melting points of 39° to 42° C. They caused death of 3 of 3 mice by repeated injections of 5 γ.

TABLE 3*

RECHROMATOGRAPHY OF THE TOXIC FRACTIONS OF CHROMATOGRAPHY I

FRACTION	ELUTED WITH 2 ML. OF:	YIELD	TOXICITY TEST			
			Amount Injected per Dose	Number of Injections	Number of Mice Dying with Typical Symptoms	Degree of Toxicity
		mg.	mg.			
1–2	Petroleum ether	traces	0.1	2	0 of 2	0
3	Petroleum ether	0				
4	Petroleum ether/ether 4:1	1.9	0.1	4	0 of 4	0
5–6	Petroleum ether/ether 4:1	traces				
7	Petroleum ether/ether 4:1	3.1	0.1	4	0 of 4	0
8	Petroleum ether/ether 1:1	0.2				
9	Petroleum ether/ether 1:1	1.0	0.1	4	1 of 4	±
10	Petroleum ether/ether 1:1	0.2				
11	Petroleum ether/ether 1:1	0.2				
12–13	Ether	traces				
14	Ether	3.0				
15	Ether	trace	0.1	3	1 of 4	±
16	Ether	0.0				
17	Ether	trace				
18	Ether/acetic acid 0.1%	0.0				
19	Ether/acetic acid 0.1%	0.6				
20	Ether/acetic acid 0.1%	0.5	0.1	3	2 of 4	+
21	Ether/acetic acid 0.1%	trace				
22	Ether/acetic acid 0.1%	0.0				
23–24	Ether/acetic acid 0.5%	traces	0.1	2	3 of 3	++
25–27	Ether/acetic acid 1.0%	traces	0.01	4	1 of 4	
28	Ether/acetic acid 5.0%	0.5	0.1	1	4 of 4	+++
			0.03	2	2 of 3	
29	Ether/acetic acid 5.0%	2.3	0.01	4	3 of 3	
			0.005	5	3 of 3	
30	Ether/acetic acid 5.0%	0.8	0.1	2	4 of 4	+++
31	Ether/acetic acid 5.0%	0.5	0.03	1	4 of 4	
32	Ether/chloroform 1:1 plus acetic acid 10%	1.0	0.1	2	1 of 3	+++
			0.01	3	2 of 3	
33–34	Ether/chloroform 1:1 plus acetic acid 10%	traces	0.1	2	2 of 4	++
			0.01	3	3 of 4	

* Symbols and footnotes as in table 2.

By repeating the chromatography with new batches of crude material, enough of the toxic product was obtained for microtitrations and qualitative nitrogen tests. The titration according to the method mentioned above gave an equivalent weight of 2,844 plus or minus 10 per cent.

The lime test for nitrogen (15) was now weakly positive, whereas no nitrogen could be detected in the less purified products.[6] This may be due to the low concentration of the N-containing constituent in the crude material. The nitrogen can be split off as ammonia by heating shortly with dilute hydrochloric acid.

The ultraviolet absorption spectra of the toxic fractions in ether solution showed two maxima:

$$213\ m\mu\ (\log \epsilon = 3.68)$$
$$268\ m\mu\ (\log \epsilon = 2.64)$$

($c = 5.0 \times 10^{-4}$ mol. per liter calculated for a molecular weight of 1,200) (figure 1).

There is an inconsistency in the data of table 3 with regard to the results of some of the biologic tests. As can be seen, the higher dilutions were, in some instances, slightly more active than the more concentrated ones. This paradox was observed several times, but, unfortunately, there was not sufficient material available to repeat the experiment on a larger number of animals. This makes it impossible to state whether the phenomenon is significant or not.

Isolation of Toxic Material from Tubercle Bacilli of the Bovine Strain Vallée

As in earlier experiments with the crude "cord factor" (2), some of the work was repeated with petroleum ether extracts from cultures of the virulent bovine strain Vallée. This strain had been propagated in this laboratory for many years, during which time its pathogenicity remained unchanged. The bacilli were cultured and extracted in the same way as organisms of the H37Rv strain. As described above, 317 mg. of the crude extract were re-precipitated from ether and extracted with hot acetone. Fifty milligrams of slightly acetone-soluble material were subjected to chromatography on silicate. The results are summarized in table 4.

As may be seen, the results are in agreement with the ones obtained with "cord factor" from the H37Rv strain. It cannot be stated whether the slight quantitative variations in the distribution of the various fractions are due to strain or to type differences.

Isolation of Toxic Material from Crude Petroleum-Ether Extracts of Six-Week-Old Cultures of H37Rv

It has been previously reported that petroleum ether extracts obtained from older bacterial cultures failed to show the characteristic "cord factor" activity which was found in extracts from younger cultures (2, 16). This observation was in good agreement with the much reduced virulence found at the same time in organisms from older cultures (17). A similar parallel between the toxicity of "cord factor" and the virulence of the bacillus was further shown to exist

[6] This positive test for nitrogen was found while the present manuscript was in preparation and after nitrogen had been determined quantitatively in a fraction of similar toxicity isolated from chloroform extracts of tubercle bacilli (5).

under cultural conditions in which the organisms were prevented from accumulating the toxic material at their cell surface or from synthesizing it (7). In any of these instances, however, the failure to demonstrate toxicity could also be due to the fact that too small a proportion of the total petroleum-ether extract was toxic. This would make it necessary to concentrate the active principle for detecting its activity under the usual testing conditions.[7] It could be antici-

TABLE 4*

CHROMATOGRAPHY OF CRUDE PETROLEUM ETHER EXTRACT FROM TWO-WEEK-OLD CULTURES OF BOVINE TUBERCLE BACILLI STRAIN VALLÉE

FRACTION	ELUTED WITH 7.5 ML. OF:	YIELD	TOXICITY TEST			
			Amount Injected Per dose	Number of Injections	Number of Mice Dying with Typical Symptoms	Degree of Toxicity
		mg.	mg.			
1-2	Petroleum ether	traces	0.1	3	0 of 3	0
3	Petroleum ether/benzene 1:1	3.1	0.1	3	0 of 5	0
4	Petroleum ether/benzene 1:1	trace				
5	Benzene	trace	0.1	3	0 of 5	0
6	Benzene	2.2				
7	Benzene/ether 1:1	trace	0.1	1	4 of 5	+++
8	Ether	12.4	0.025	2	4 of 5	
9	Ether	3.1	0.1	2	4 of 5	+++
			0.025	3	3 of 5	
10	Ether	2.5	0.1	2	4 of 5	+++
11	Ether/acetic acid 5%	10.3	0.1	2	5 of 5	+++
			0.012	4	5 of 5	
12	Ether/acetic acid 5%	11.0	0.1	2	5 of 5	+++
			0.012	4	3 of 5	
13	Ether/acetic acid 5%	4.0	0.1	2	4 of 5	++
14-18	Ether/acetic acid 5%	traces	0.1	3	3 of 5	+
19-22	Ether/acetic acid 10%	traces	0.1	3	4 of 5	++
23-28	Ether/acetic acid 10%, methanol 10%	traces	0.1	3	5 of 5	++
			0.025	5	2 of 5	

* Symbols and footnotes as in table 2.

pated that this was true with extracts from older cultures in which the presence of toxic material derived from the relatively few young organisms present in old cultures could be masked by the large quantities of nontoxic waxes extracted from the masses of old bacilli.

To test this hypothesis, a petroleum ether extract was prepared from six-week-old cultures of H37Rv, and 2.1 gm. of this crude material was chromatographed on silicate in the usual manner. A summary of the results is shown

[7] The highest doses tested were five injections of 0.1 mg. each (7). This is an arbitrary limit, but a line had to be drawn somewhere for the daily routine of testing samples.

in table 5. It can be seen that, although the highest doses of crude material which were tested in mice did not show any toxicity, such activity was found after effective concentration. It was present in the same chromatographic fractions which contained the toxic material in comparable extracts from younger cultures.

TABLE 5*

CHROMATOGRAPHIC CONCENTRATION OF TOXIC MATERIAL FROM PETROLEUM ETHER EXTRACTS OF SIX-WEEK-OLD CULTURES OF M. TUBERCULOSIS VAR. HOMINIS H37Rv

FRACTION	AMOUNT INJECTED PER DOSE	NUMBER OF INJECTIONS	NUMBER OF MICE DYING WITH TYPICAL SYMPTOMS	DEGREE OF TOXICITY
	mg.			
Crude petroleum ether extract	0.1	5	0 of 5	0
Pool of the chromatographic fractions eluted with petroleum ether	0.1	5	0 of 5	0
Pool of the chromatographic fractions eluted with ether/acetic acid	0.1	4	3 of 5	+

* Symbols and footnotes as in table 2.

DISCUSSION

The experiments reported in the present paper are an attempt to use the characteristic toxicity of crude petroleum-ether extracts from virulent tubercle bacilli as a lead throughout the work of chemical purification. An attempt was made in earlier experiments to compare in a given strain of tubercle bacilli the activity of "cord factor" with its pathogenicity. Under various experimental conditions, the two properties were found to be closely associated (7, 17). This was suggestive of a certain, yet still undefined, part played by "cord factor" in the pathogenic function of the tubercle bacillus, but it is not known whether this role can also be attributed to the toxic component of the extract alone. This question can be clarified only by further experiments with the purified compound and will not be discussed in the present paper.

Despite the lack of information concerning the role of the toxic fraction, there were several reasons for trying to separate it from the various other compounds which are present in the crude extract. Provided mild chemical methods are used, the toxic component can be concentrated and purified without significant loss of activity. The characteristic biologic properties of the toxic component are a useful experimental tool for directing the course of the chemical work. The toxicity of the fraction lends itself, not only for qualitative, but also for quantitative, tests. This is an important point when the problem of concentrating a compound arises. Finally, the biologic assay is easy to carry out and the method gives reproducible results.

Other fractions obtained in the course of this work were also studied and some of them have been chemically identified (13), but no characteristic biologic tests are available for their biologic identification. Moreover, it is reasonable to assume that a bacterial constituent of such high degree of toxicity cannot be

entirely without function in the life of the bacillus. The relatively small amounts of toxic material which are obtainable from the bacterial cultures do not necessarily contradict this assumption. A rough calculation shows that, with the present methods of extraction, approximately 10^{-9} γ of toxic material can be isolated from each tubercle bacillus. This represents approximately one ten-thousandth of the bacterial weight, or approximately 10^6 molecules of toxic material per cell. If the view be accepted that this fraction is constantly being produced and released by the bacterial cells (2, 7), the amounts calculated from these crude data lie well within the order of magnitude of other biologic products of comparable activity.

No attempt was made in the present study to provide further information on the possible role played by "cord factor" and its toxic component during the course of infection. The present and the two succeeding papers deal exclusively with the occurrence and some of the chemical properties of this component. It was found to be present in all petroleum ether extracts from young cultures of virulent organisms and of BCG. Smaller amounts were also found in extracts from old surface cultures, but there the toxicity was only detected after the material was sufficiently concentrated and separated from the bulk of nontoxic constituents. The low concentration of toxic material in extracts from old bacteria accounts for the failure in previous experiments (2) to detect toxicity in crude preparations. It may also account for the failure of Philpot and Wells (1) to repeat the experiments of the present writers with success. In their paper, Philpot and Wells do not give any information on the age of the cultures they extracted. The present writers have repeatedly stressed the point that young cultures have to be used if crude extracts are used for biologic experimentation (2, 16). Since Philpot and Wells did not test single doses larger than 0.1 mg., they could have failed to attain the threshold concentration which is necessary for a toxic response. Moreover, they do not state that they weighed the animals during the course of their experiments. The drop of weight that follows each injection of active material is a characteristic and very sensitive index of the activity of the injected material (2, 7). Finally, the strains of mice they used may not have been very susceptible. Differences between various mouse strains have been reported earlier (2) and are confirmed in the present paper (table 1). Philpot and Wells do not specify the age, sex, and origin of their "Laboratory white mice, C 57 Black mice, and dba mice." It is common knowledge that great differences exist between various breeds of so-called identical strains of laboratory animals.

All attempts at the identification of the toxic fraction were seriously hampered throughout the present study by the scarcity of the available material which represents only approximately one ten-thousandth of the original bacterial growth. All material which showed toxicity had a characteristic UV absorption at λ max. = 213 mμ, and the higher purified fractions an additional one at λ max. = 268 mμ, which could be due to a keto-group. There was no parallel, however, between the intensity of these absorptions and the degree of toxicity.

It is noteworthy that the more toxic chromatographic fractions contained nitrogen. The failure to detect nitrogen in less purified products is most likely

due to the low concentration of the nitrogen-containing compound in the cruder preparations. In a succeeding paper (5), results are reported which show the presence of nitrogen also in toxic fractions isolated from tubercle bacilli by a different method.

An appreciable degree of acidity was present in all toxic fractions, whether crude or purified; e.g., table 3, fractions 28 to 31. Organic acids could be detected by both the hydroxamate method and by microtitration. Thus, the active product seems either to be an acid itself or to be contaminated with an organic acid. This point is further discussed in a succeeding report (5).

SUMMARY

The chemical purification of a toxic component of the tubercle bacillus is described. The crude material which is obtained from bacterial cultures by extraction with petroleum ether is effectively concentrated by chromatography on activated magnesium silicate. The toxic fraction represents only a small proportion of the total extract. Like the crude material, it is toxic for mice upon repeated intraperitoneal injections. Some of the chemical properties of purified fractions are described. The most toxic fraction obtained so far was lethal for mice upon five repeated injections of 0.005 mg. each. The mice died within one to two weeks after the first injection with extended characteristic pulmonary hemorrhages. Previous observations on varying susceptibility in different strains of mice are confirmed.

SUMARIO

Componente Lípido Tóxico del Bacilo Tuberculoso ("Factor Cord"): I. Aislamiento de los Extractos Obtenidos con Eter de Petróleo de Cultivos Bacterianos Jóvenes

Descríbese la purificación química de un componente tóxico del bacilo tuberculoso. La substancia cruda obtenida de cultivos bacterianos por extracción con éter de petróleo es concentrada eficazmente por la cromatografía sobre silicata de magnesio activado. La fracción tóxica no representa más que una pequeña proporción del extracto total. Lo mismo que la substancia natural, es tóxica para los ratones en inyecciones intraperitoneales repetidas. Descríbense algunas de las propiedades químicas de las fracciones purificadas. La fracción más tóxica obtenida hasta ahora resultó letal para los ratones con cinco inyecciones repetidas de 0.005 mg. cada una. Los ratones murieron en término de una a dos semanas de la primera inyección, con extensas y típicas hemorrhagias pulmonares. Confírmanse observaciones anteriores acerca de la diversa susceptibilidad mostrada por distintas cepas de ratones.

RESUME

Un composant toxique lipidique du bacille tuberculeux ("Cord Factor"): I. Isolement par extraction avec l'éther de pétrole à partir de cultures bactériennes jeunes

La purification chimique d'un composant toxique du bacille de Koch est décrite. La substance brute est extraite de cultures jeunes par l'éther de pétrole, puis concentrée par chromatographie sur du silicate de magnésium activé. La fraction toxique ne représente qu'une petite proportion de l'extrait total. De même que la substance brute, elle se montre toxique pour la souris à la suite d'injections intrapéritonéales répétées. Certaines des propriétés chimiques des fractions toxiques purifiées sont décrites. Chez la souris, cinq injections de 0,005 mg. de la fraction la plus toxique ont provoqué la mort. L'animal a succombé une à deux semaines après la première injection avec des signes caractéristiques d'hémorragies pulmonaires étendues. Les observations antérieures sur les différences de sensibilité selon les souches sont confirmées.

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FURTHER OBSERVATIONS ON THE PHARMACOLOGY OF ISONIAZID[1]

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INTRODUCTION

In a previous report (1) the acute, subacute, and chronic toxicity of the antituberculous compound isonicotinic acid hydrazide, generically designated as isoniazid, was described by the present writers for mice, rats, and dogs, respectively. The acute intravenous LD_{50} dose in unanesthetized dogs was approximately 50 mg. per kg., death being preceded by repetitive clonic and tonic convulsions, whereas the chronic orally tolerated dose was approximately 10 mg. per kg. per day.

The preliminary findings in experimental animals further indicated that, at the equivalent of therapeutic doses, neither isoniazid (1, 2, 3) nor its isopropyl derivative (1-isonicotinyl-2-isopropyl hydrazine), generically named iproniazid (2), possessed general pharmacodynamic effects. A series of minor clinical side effects in the therapy of human tuberculosis were reported with daily oral doses ranging from 2 to 10 mg. per kg., and the suggested explanation (4, 5, 6) was that some of these effects might be of autonomic origin and due to either sympathetic stimulating or parasympathetic blocking properties of these drugs. Other clinical groups working with isoniazid alone, however, obtained little or no evidence of such autonomic dysfunction (7, 8, 9).

The purpose of the present report is to examine further experimentally whether isoniazid or iproniazid, at the equivalent of therapeutic doses or concentrations, manifests autonomic or other pharmacodynamic effects which possibly could be related to either one or more of the reported clinical side effects in tuberculous patients.

OBSERVATIONS

Cardiovascular: Six unanesthetized and 17 anesthetized mongrel dogs, ranging in body weight from 7.1 to 14.2 kg., were used to study the effects of isoniazid and iproniazid on the cardiovascular system and respiration.

In some instances local anesthesia (1 per cent Intracaine) was employed for insertion of femoral arterial and venous cannulae in otherwise unanesthetized dogs. Fifteen dogs were anesthetized with morphine, 0.5 to 1.0 mg per kg., subcutaneously, and urethane, 1.0 to 1.5 gm. per kg., intravenously. In these animals one or both vagi were severed cervically and atropine, 0.5 to 1.0 mg. per kg., was administered intravenously to part of the latter group.

Single or cumulative intravenous doses of isoniazid or iproniazid were administered to these dogs, each injection being given during a period of fifteen to thirty seconds. The

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intravenous drug doses were commonly 1, 2, 4, 8, 16, and 32 mg. per kg.; injections were generally made at twenty-minute intervals before and after the appropriate measurements or test responses indicated below.

In nearly all instances systemic blood pressure from a carotid or femoral artery was recorded continuously on a kymograph with a calibrated bellows-type manometer. In the absence of electrocardiographic recording, the heart rate was measured in some of these dogs with a stethoscope. In several of the anesthetized dogs, the rate and force of respiration was recorded from a tracheal cannula. Electrocardiographic tracings (lead II) and records of basal metabolic rate were obtained at regular intervals from some of the unanesthetized dogs. At repeated intervals other unanesthetized animals were subjected to a tilt procedure which consisted of a one-minute head-up position 85 degrees from the horizontal. Standard intravenous injections of *l*-epinephrine, acetylcholine, and histamine ranging from 1 to 8γ per kg., but kept constant within each animal, were administered to unanesthetized and anesthetized dogs. In one group of anesthetized and unilaterally vagotomized dogs these low doses of acetylcholine were given before and after cardiac arrest induced by uniform electrical stimulation of the peripheral end of the severed vagus nerve for five-second periods. High doses of acetylcholine (0.15 to 0.50 mg. per kg.) were administered intravenously to the anesthetized dogs which were both atropinized and bilaterally vagotomized. In these dogs the carotid arteries were isolated and occluded for forty-five-second periods at regular intervals. Hind leg volume of vagotomized, anesthetized dogs was recorded mechanically via a plethysmograph.

With the intravenous doses previously indicated, isoniazid manifested little or no effect upon any of the test responses measured or elicited. Emesis and convulsions were observed in unanesthetized dogs after a cumulative total dose of 63 mg. per kg. although, prior to the development of acute toxicity, blood pressure, heart rate, the electrocardiogram, and metabolic rate remained essentially unchanged.

The results with iproniazid were similarly negative except that, with doses of 8 mg. per kg. and higher, immediate transient depressor responses accompanied by a slight tachycardia were observed. Intravenous pretreatment with atropine, 0.5 mg. per kg., or diphenhydramine hydrochloride, 8 mg. per kg., had little or no effect on the depressor response produced by the intravenous injection of 16 mg. of iproniazid per kg. in vagotomized, anesthetized dogs. The average changes in systemic blood pressure produced by isoniazid and iproniazid in unanesthetized and anesthetized dogs are shown in table 1.

One group of 4 vagotomized dogs under morphine-urethane anesthesia received both intravenous and intra-arterial injections of isoniazid or iproniazid.

Continuous kymograph recordings of systemic (carotid) blood pressure and peripheral back pressures in one normal leg and one denervated leg were conducted according to the three-manometer technique of Nolf (10) similar to that described by Walker and his coworkers (11) except that all intra-arterial drug injections were made into the normal leg only. Each intra-arterial injection was preceded and followed by injections of equal volumes (0.15 to 0.60 ml.) of physiologic saline solution. Each dog received, at twenty-minute intervals, isoniazid or iproniazid in doses of 0.06, 0.25, 1.0, 4.0, and 16.0 mg. per kg. intra-arterially and then 16 mg. per kg. intravenously.

With none of the above doses did isoniazid produce acute changes in systemic blood pressure or in peripheral back pressure in the denervated leg, and only with intra-arterial doses of 4.0 and 16.0 mg. per kg. did isoniazid produce an

average decrease of 13 per cent in the normal leg back pressure for a period of approximately twenty seconds.

In contrast, intra-arterial injections of iproniazid at 0.25 to 16.0 mg. per kg. produced maximum decreases of 18 per cent for six minutes in systemic blood pressure, 16 per cent for two minutes in peripheral back pressure in the denervated leg, and as much as 64 per cent for three minutes in the normal leg back pressure. The intravenous injection of 16 mg. per kg. of iproniazid produced decreases of 25 to 30 per cent for four minutes in systemic blood pressure and for two minutes in back pressure of either leg.

Cutaneous vascular bed: The effects of isoniazid and iproniazid on the cutaneous vascular bed were studied by the trypan blue technique in albino rabbits. A total of 93 randomized intracutaneous injections (0.2 ml. volumes) were made

TABLE 1

EFFECTS OF ISONIAZID AND IPRONIAZID ON SYSTEMIC BLOOD PRESSURE OF UNANESTHETIZED AND ANESTHETIZED DOGS

INTRAVENOUS DOSE	AVERAGE PER CENT MAXIMUM CHANGE IN SYSTEMIC BLOOD PRESSURE	
	Isoniazid	Iproniazid
mg. per kg.		
1	−0.2 (7)	−0.8 (5)
2	−0.2 (7)	−1.9 (6)
4	−0.1 (8)	−2.8 (6)
8	−0.3 (7)	−6.0 (5)
16	+0.7 (11)	−17.0 (11)
32	−0.9 (7)	−22.2 (5)

Number in parentheses equals total number of dogs; in each instance 2 dogs were unanesthetized and the remainder were anesthetized.

into the shaved abdominal skin of 6 rabbits, followed immediately by 10 ml. of 1 per cent aqueous solution of trypan blue injected intravenously into each rabbit. Reference cutaneous vasodilatation and increased capillary permeability (bluing) were produced by intracutaneous injections of histamine phosphate at concentrations of 10, 100, and 1,000 γ per ml. as base; local vasoconstriction (blanching) was produced with similar injections of *l*-epinephrine bitartrate at concentrations of 1, 10, and 100 γ per ml. as base in each of 3 rabbits.

Intracutaneous injections of isoniazid and iproniazid in these same animals were made with solutions containing 1, 10, 100, and 1,000 γ per ml. of either drug. Physiologic saline controls were included in each series, and observations were made five, ten, twenty, and forty minutes after the injection of the dye. The wheals produced by either isoniazid or iproniazid were essentially indistinguishable from the saline control injections. The other 3 rabbits received intracutaneous injections of saline, of the three concentrations of histamine alone, of the three lower concentrations of isoniazid alone, and of the nine possible combinations of histamine plus isoniazid. Trypan blue was injected as indicated previously. Little or no difference in the degree of dye localization was obtained between histamine alone and histamine plus isoniazid.

Bladder and ileum: In dogs anesthetized with pentobarbital sodium, 30 mg. per kg. intravenously, activity of the ileum and bladder *in situ* were recorded kymographically. Tambours were connected to the bladder according to the method described by Jackson (12) and to a balloon inserted via laparotomy into the ileum under approximately 7 cm. of hydrostatic pressure. Intravenous injections of isoniazid or iproniazid, within a dose range of 1 to 32 mg. per kg., were without apparent effect on spontaneous movements of the ileum and bladder.

The *in vitro* effects of isoniazid and iproniazid on isolated rabbit and guinea pig ileum were studied separately in tenfold concentration steps from 1 to 1,000γ per ml. on a total of twelve muscle strips, each suspended in Tyrode's solution in a 50 ml. chamber with the usual kymographic recording. Two to four minutes of antituberculous drug pretreatment or post-treatment was employed with the spasmogenic or spasmolytic agents indicated below.

Both isoniazid and iproniazid reduced the amplitude of spontaneous contractions of rabbit ileum only at the highest concentration, although little or no effect was observed on tone. In counteracting acetylcholine-induced spasm of isolated rabbit and guinea pig ileum, iproniazid manifested approximately 1/33,000 to 1/100,000 the activity of atropine sulfate, whereas isoniazid was even less effective. Neither drug augmented the inhibitory effect of *l*-epinephrine bitartrate on isolated rabbit intestine except for equivocal results at concentrations of 1,000 γ per ml. On guinea pig ileum *in vitro*, isoniazid and iproniazid manifested inhibitory action against histamine- and barium-induced spasm similar to that shown by each against acetylcholine. Since, in these same preparations, atropine manifested its usual specificity for blocking acetylcholine-induced spasm, it would appear that the smooth muscle inhibitory effects obtained with these drugs at extremely high concentrations were relatively nonspecific and not atropine-like in nature.

Analgesia: Isoniazid and iproniazid were tested for analgetic effects in rats by a modification of the D'Amour-Smith method similar to that employed experimentally and biometrically by Bonnycastle and Leonard (13). A total of 60 male albino rats ranging in body weight from 200 to 300 gm. received oral doses of 31, 62, 125, 250, and 500 mg. per kg. of either isoniazid or iproniazid. Reaction time determinations were made at twenty-minute intervals. Neither drug produced analgesia at nonlethal oral doses within a two-hour period after dosage.

DISCUSSION

The results presented herein both confirm and extend those previously reported for isoniazid (1, 2, 3) and for iproniazid (2). In experimental animals, intravenous doses of these drugs corresponding to human daily oral doses (1 to 10 mg. per kg.) or *in vitro* drug concentrations equivalent to human plasma drug concentrations (approximately 1 to 10 γ per ml.) manifested little, if any, parasympathetic blocking, sympathetic stimulating, or other general pharmacodynamic properties.

Thus, in unanesthetized and anesthetized dogs, isoniazid had little or no effect on systemic blood pressure, heart rate, electrocardiogram, metabolic rate, hind leg volume and peripheral resistance, or spontaneous activity of ileum and

bladder *in situ*. Little or no effect was observed on the typical blood pressure response to carotid occlusion, vagal stimulation, nicotinic doses of acetylcholine, and to injections of acetylcholine, epinephrine, and histamine. No evidence for postural hypotension was obtained. No effect was discernible on the local vascular bed after intracutaneous injection of isoniazid in the rabbit nor did it appear to alter dye localization produced by histamine. *In vitro* concentrations of isoniazid required to inhibit spontaneous gut activity or tone were at least 100 to 1,000 times greater than that likely to be found in circulating plasma of man under present dosage regimens, and even then no evidence for atropine-like specificity was indicated.

Similar testing with iproniazid also yielded essentially negative results with one exception. Intravenous doses of 8 mg. per kg. or higher of this isopropyl derivative in unanesthetized and anesthetized dogs consistently resulted in transient depressor responses. The mechanism of this hypotensive effect remains to be determined. The preliminary results obtained herein suggest that, in the dog, decreases in vascular resistance in the extremities play a relatively minor role after intravenous injection of iproniazid. Furthermore, this hypotensive effect appeared to be neither muscarinic nor histamine-like in nature, nor did it appear to be related to any cardiotoxicity as evaluated by electrocardiogram. Although a few clinical observations of hypotension or possibly related vertigo have been reported (4, 5) for both drugs, the experimental data obtained herein indicated that only iproniazid produced even transient hypotension in the dog.

None of the experimental results in animals reported herein or by others (1, 2, 3) explain reports of clinical side effects such as dryness of the mouth, dyspnea, constipation, urinary retention (4, 5), or peripheral vasospasm (6). Furthermore, other clinical investigators (7, 8, 9) found few, if any, signs of drug toxicity involving cardiovascular or autonomic functions during therapy with isoniazid.

Clinical side effects such as insomnia, twitching of the extremities, tremors of limbs, and hyper-reflexia have been encountered more commonly (4, 5, 9, 14, 15, 16, 17). If these particular side effects are directly related to dosage with either isoniazid or iproniazid, it is possible at this time to speculate that these symptoms represent minimal evidence of the central stimulant action of these drugs. Preliminary results with isoniazid in mice have suggested indirectly that this stimulation is fairly widespread in locus since an acutely toxic dose of isoniazid reduced the convulsive dose of metrazol only slightly more than that of strychnine (18). Should this central stimulant action prove to be potentially serious in therapy, e. g., in patients with known or suspected convulsive tendencies, laboratory evidence (3, 19, 20) has indicated that barbiturates and related central depressant agents could probably be employed to good effect as pharmacologic antagonists.

The D'Amour-Smith method, as employed in this laboratory, detects analgesia produced by drugs ranging from acetylsalicylic acid to the addicting narcotics. When similarly tested in rats, neither isoniazid nor iproniazid produced analgesia with nonlethal doses. On an empirical basis alone, it would appear likely that the systemic beneficial effects reported (6) for isoniazid in nontuber-

culous patients with carcinoma are not related to analgesia demonstrable in the rat.

SUMMARY

In experimental animals, isoniazid did not manifest general pharmacodynamic effects with the equivalent of therapeutic doses or concentrations. In dogs, isoniazid did not affect respiration, metabolic rate, systemic blood pressure, heart rate, electrocardiographic tracings (lead II), hind leg volume or peripheral resistance, nor did it produce postural hypotension. The pressor effect and bradycardia produced by epinephrine were essentially unaltered by isoniazid. The drug had little or no effect on the depressor response produced by injections of either acetylcholine or histamine. No evidence for adrenomedullary or vagal stimulating or blocking action was obtained in the dog. Intracutaneous administration of isoniazid in rabbits produced little or no effect on the cutaneous vascular bed with trypan blue visualization, nor did it alter the dye localization produced by histamine. No effect was obtained on spontaneous activity of dog ileum or bladder *in situ*, nor was atropine-like or other spasmolytic activity detected on isolated rabbit and guinea pig ileum. No analgesic effects were observed in rats.

Essentially similar results were obtained with iproniazid, except that, with intravenous doses of 8 mg. per kg. or higher, transient hypotension and tachycardia were observed.

SUMARIO

Nuevas Observaciones sobre la Farmacología del Isoniazid (Isoniacida)

En los animales de experimentación, el isoniazid no manifestó efecto farmacodinámico con el equivalente de dosis o concentraciones terapéuticas. En los perros, el isoniazid no afectó la respiración, el coeficiente metabólico, la tensión sanguínea general, la frecuencia cardíaca, el electrocardiograma (Derivación II), el volumen de la pata trasera o la resistencia periférica, ni tampoco produjo hipotensión postural. El efecto presor y la bradicardia producidos por la epinefrina permanecieron substancialmente inalterados. La droga ejerció poco o ningún efecto sobre la respuesta depresiva producida por las inyecciones ya de acetilcolina o de histamina. No se observaron, en el perro, signos de estímulo o bloqueo suprarrenomedular o neumogástrico. La administración intracutánea de isoniazid en los conejos produjo poco o ningún efecto sobre el lecho vascular cutáneo, al ser visualizado con azul de trípano y no alteró la localización del colorante producida por la histamina. No se obtuvo ningún efecto sobre la actividad espontánea del íleon o la vejiga *in situ* del perro, ni se descubrió actividad atropinoidea o espasmolítica en otra forma en el íleon aislado del conejo y del cobayo. No se observaron efectos analgésicos en las ratas.

Obtuviéronse resultados en el fondo semejantes con el iproniazid, excepto que, con dosis intravenosas de 8 mg. por kg. o mayores, se notaron hipotensión y taquicardia pasajeras.

RESUME

Nouvelles observations sur la pharmacologie de l'isoniazide

Chez l'animal en expérience, l'isoniazide n'a déterminé aucune action pharmacodynamique générale lorsque l'équivalent de doses ou concentrations thérapeutiques a été administré. Chez le chien, l'isoniazide n'a pas modifié la respiration, le taux du métabolisme, la pression artérielle, le rythme cardiaque, l'électrocardiogramme (tracé II), le volume de

la patte arrière, la résistance périphérique, ou l'hypotension de posture. L'effet presseur et la bradycardie produits par l'adrénaline n'étaient pas modifiés de façon fondamentale. Le médicament n'avait que peu ou pas d'effet sur la réaction de dépression provoquée par l'injection d'acétylcholine ou d'histamine. Aucune preuve d'une action stimulatrice ou inhibitrice médullo-surrénale ou vagale n'a été obtenue chez le chien. Chez le lapin, l'administration intracutanée d'isoniazide n'a produit que peu ou pas d'effet sur la circulation vasculaire cutanée examinée par la méthode du bleu-trypan; la localisation du colorant produite par l'histamine n'a pas été modifiée. Aucune modification *in situ* de l'activité spontanée de l'iléon ou de la vessie du chien n'a été obtenue; de même, on n'a pas observé d'action analogue à celle de l'atropine ou autre effet spasmolytique sur l'iléon isolé du lapin et du cobaye. Aucun effet analgésique n'a été observé chez le rat.

Des résultats essentiellement semblables ont été obtenus avec l'iproniazide; toutefois, avec des doses intraveineuses de 8 mg. par kg. ou plus, l'hypotension et une tachycardie temporaires ont été observées.

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THE LONG-TERM TOXICITY AND METABOLIC EFFECTS OF ISONIAZID IN ADULTS[1, 2]

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INTRODUCTION

A concerted study has been conducted upon 10 adult patients with advanced pulmonary and renal tuberculosis to determine the toxic and metabolic effects which isoniazid might have when administered for six continuous months. It has been reported by Elmendorf and his associates (1) and by others (2, 3, 4) that hematologic, hepatic, renal, and nervous system defects do not develop with doses of isoniazid of 5 mg. per kg. of body weight daily for three months. The present report describes the results of detailed laboratory studies performed periodically and frequently for six months of continuous therapy with isoniazid.[3]

PLAN OF INVESTIGATION

Ten patients with advanced progressing pulmonary tuberculosis were given 4 to 5 mg. of isoniazid per kg. of body weight in two divided oral doses at twelve-hour intervals. Total daily doses of 200 to 350 mg. per day were continued for six months or until death, and no dose was omitted. The subjects were examined daily for evidences of toxicity and for other clinical reasons.

The laboratory studies were divided into two three-month intervals. During the first period, weekly determinations of the following values were performed: fasting blood sugar, serum nonprotein nitrogen, prothrombin time, erythrocyte sedimentation rate, routine urinalysis, complete blood counts, and hematocrits. Sputum was examined once every other week for gross estimation of tubercle bacillary counts. At monthly intervals the values for serum proteins with albumin-globulin ratios and serum sodium and potassium were determined. During the second three months of the study all of the above-mentioned chemical constituents of the blood were measured at approximately monthly intervals (table 1).

From all of these laboratory examinations the effects of isoniazid upon the function of the liver, kidney, bone marrow, and the endocrine glands were evaluated. Clinical examinations included periodic gross neurologic tests to ensure the possible diagnosis of central nervous system irritation from the agent, as well as frequent physical examinations.

RESULTS

Effects upon Bone Marrow Function

Eight of the 10 subjects had normal hematocrits at the start of the study. In one it was 37 per cent and in the other 54 per cent. In no instance was a change

[1] From the Department of Medicine, State University of New York, College of Medicine at Syracuse, New York; and the State of New York Onondaga Sanatorium, Syracuse, New York.

[2] Portions of this study were supported by grants from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association; and from the Bristol Laboratories, Inc., Syracuse, New York.

[3] All isoniazid used in this study was generously supplied as Cotinazin by Dr. G. L. Hobby, Chas. Pfizer & Co., Brooklyn, New York.

from pretreatment levels observed. No trend was noted in serial erythrocyte, leukocyte, and lymphocyte counts. Although all of the 10 subjects had, at one time or another during the six months, total leukocyte counts in excess of 10,000 per cubic milliliter, no significant shift in type of cell was observed with these episodes.

Comment: The effects of isoniazid upon bone marrow function were not significant; certainly no depression or stimulation occurred.

Effects upon Kidney Function

Seven of the 10 patients had normal urinary constituents and sediment throughout the period of study. One patient was found to be excreting a trace of albumin for one week during the second week of the study. This cleared without specific remedy, did not recur, and its significance cannot be evaluated. Another patient was known to have had nontuberculous kidney disease for many years. At the start of the study he was excreting excessive amounts of albumin in the urine and an abnormal number of casts. During the study no change in these abnormalities occurred. The last patient died after eighty-one days from kidney failure due to tuberculosis. Throughout the study her kidney function neither improved nor was there a slowing of the gradual deterioration in her state of uremia, which had been progressive in the pretreatment period. The blood serum at death contained more than 70 γ of isoniazid per ml. This represents, of course, an extraordinarily high concentration of drug. It is not possible to state that the patient had concentrations of this order at any other time during life, and it is well appreciated that a concentration of 70 γ is a potentially dangerous level. Her nonprotein nitrogen concentration gradually rose during the therapy period but the upward trend presumably had been established prior to the start of isoniazid. Gross and microscopic examinations of both kidneys after autopsy failed to reveal any possible toxic effect of isonazid upon the generalized extensive caseous tuberculosis present in both kidneys.

Serial determinations of nonprotein nitrogen in one other person revealed minor but abnormal variations. His pretreatment nonprotein nitrogen value was 31 mg. per 100 ml. It remained above this level throughout the first five months of treatment and on one occasion (fifth week) rose to 46 mg. per 100 ml. However, despite continuation of the drug it fell to 30 mg. per 100 ml. before the end of the six months and remained at that level for the next month.

Comment: The effect of isoniazid upon kidney function was negligible in the presence of previously established renal disease, and there was no indication that it had any deleterious effect upon normal kidneys.

Hepatic Function

Only two specific liver function tests were performed in each patient. Prothrombin times and total proteins with albumin and globulin ratios were normal in the 10 patients at the start of the study, and no variations from the normal values were observed at any time during the six months of isoniazid therapy. Although not specifically a measure of liver function, the erythrocyte sedimentation rate done serially revealed data of interest. The rate of fall of erythrocytes

became either less rapid or was variable in 6 of the 10 patients during the therapy period although in none of the 6 did the rate fall to a normal range. The initially abnormally high erythrocyte sedimentation rates in 2 patients did become normal during the treatment period. The sedimentation rates in the 2 remaining patients slowed during the first three months of treatment, then became more rapid as therapy was continued.

Comment: There was no evidence that isoniazid deleteriously affected the synthesis of either prothrombin or of proteins in general—two acceptable measures of over-all liver function.

Effect upon Metabolism and Electrolytes

Fasting blood sugar values and concentrations of serum sodium and potassium were in no way altered from the normal range. Although hyponatremia has been described in chronic progressive phthisis, in no patient in the present series was that evident. It cannot be stated, therefore, what effect isoniazid might have upon a patient with a slow serum sodium.

Endocrine System

Gross clinical evidences of malfunction of adrenal, thyroid, genital, and pancreatic glands were never manifested during the six months of observation. No precise laboratory tests of function of these endocrine glands were, however, performed. The close daily clinical observations made upon each patient would presumably have revealed significant effects upon those glands if any had occurred.

Effects upon Central Nervous System and Other Miscellaneous Observations

No specific neurologic defect occurred during the six-month treatment period. Three patients had subjective symptoms referable to the central nervous system, but in no person was the syndrome recognizable as suggesting specific abnormality of the nervous system. One patient complained intermittently of cephalgia and he had mild subjective muscular twitchings which were generalized. All electrolyte levels were normal, no abnormal neurologic findings became manifest, and both symptoms disappeared after one month; they did not recur. The second patient noted circumoral numbness and paresthesias of her extremities which were inconstantly present throughout the period. Slight twitchings of both legs were also perceived by the patient; these also disappeared after cessation of treatment. All examinations were normal in this patient. The patient who died in uremia also complained of muscular twitching and severe weakness during the period of therapy. She developed deep tendon hyperreflexia and some gross tremors preterminally. All of these possible manifestations of drug toxicity were presumably the result of her failing kidneys and the syndrome of uremia and were not due to isoniazid (table 1).

In general, all of the patients received isoniazid in good humor and without complaint. Had there been fewer examinations and questionings, the mild subjective complaints in the 2 patients would not have been recognized, nor would the physicians' concern have been as marked.

One patient developed slight urticaria which persisted fairly constantly after the first month of drug therapy. It ceased promptly upon discontinuance of therapy after 180 days. No eosinophilia was noted, the patients' complaints were minor, no alteration of dosage was deemed necessary, the lesions did not spread, and it cannot be proved that the skin lesions were due specifically to isoniazid (table 1).

Comment: No neurologic abnormalities developed as a result of six months of treatment with isoniazid. Subjective complaints of headache, muscular twitchings, circumoral numbness, and vague paresthesias were noted by 3 patients but none precluded continuation of therapy, and no untoward aftereffects developed.

TABLE 1

TOTAL LABORATORY TESTS MADE IN TEN TUBERCULOUS SUBJECTS WHO RECEIVED ISONIAZID FOR SIX MONTHS

TYPE	APPROXIMATE NUMBER OF DETERMINATIONS MADE	PRETREATMENT DETERMINATIONS		POST-TREATMENT DETERMINATIONS	
		Normal	Abnormal	Normal	Abnormal
Blood sugar	127*	10	0	10	0
Nonprotein nitrogen	127*	9	1	9	1
Prothrombin time	127*	10	0	10	0
Erythrocyte sedimentation rate	127*	0	10	2	8
Urinalysis	228†	8	2	8	2
Complete blood count	174‡	8	2	8	2
Hematocrit	174‡	8	2	8	2
Total proteins	39§	10	0	10	0
Albumin-globulin ratio	39§	10	0	10	0
Serum sodium	39§	10	0	10	0
Serum potassium	39§	10	0	10	0

* Weekly first 12 weeks—monthly second 12 weeks.
† Weekly throughout 24 weeks.
‡ Weekly first 12 weeks—fortnightly second 12 weeks.
§ Monthly first 12 weeks—every two months second 12 weeks.

One patient developed mild urticaria during the six months in which she received isoniazid.

SUMMARY

Periodic clinical and laboratory observations were made for a six-month period in 10 patients who received 5 mg. of isoniazid per kg. per day. The results reaffirm that isoniazid is a safe drug and, in the dosage used, can be continued for at least six months without apparent damage to the functions of human liver, kidneys, bone marrow, and central nervous system. Furthermore, in one instance of fatal renal tuberculosis, the standard 5 mg. per kg. dose of isoniazid neither altered the clinical disease nor changed in any way the microscopic picture of the autopsied organs. In one instance, urticaria developed which was not serious, and it did not require cessation of the drug.

SUMARIO

Estudio de la Toxicidad y los Efectos metabólicos a Largo Plazo del Isoniazid en Personas Adultas

Las observaciones de laboratorio que acompañaron a este estudio reafirman que el isoniazid es una droga inocua y que, a las dosis utilizadas, puede administrarse a lo menos seis meses sin daño aparente de las funciones del hígado, de los riñones, la médula ósea y el sistema nervioso central en el hombre. Además, cuando existe tuberculosis renal letal, la dosis corriente de 5 mg. por kg. no altera la afección ni modifica en modo alguno el cuadro microscópico de los órganos autopsiados. En un caso, se presentó urticaria, que no fué grave, ni requirió el cese de la medicación.

RESUME

Etude, chez l'adulte, de la toxicité à longue échéance et des effets métaboliques de l'isoniazide

Les observations de laboratoire jointes à cette étude confirment que l'isoniazide est un médicament sûr, dont l'administration aux doses usuelles, chez l'homme, peut être poursuivie pendant au moins six mois sans altération apparente des fonctions du foie, du rein, de la moelle osseuse et du système nerveux central. De plus, en présence d'une tuberculose rénale fatale, la dose standard de 5 mg. par kg. ne modifie pas l'aspect clinique de l'affection et ne change d'aucune manière l'anatomie pathologique des organes prélevés après autopsie. Dans un cas il s'est produit del'urticaire; celle-ci n'était pas grave, et n'a pas nécessité l'interruption de la médication.

Acknowledgment

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THE SPECIFICITY OF THE HEMAGGLUTININ ADSORPTION TECHNIQUE IN THE SEROLOGIC STUDY OF TUBERCULOSIS[1]

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INTRODUCTION

The hemagglutination test as described by Middlebrook and Dubos (1) with its later modifications (2, 3) introduced a new serologic technique for studying the tubercle bacilli which simplifies or eliminates many of the problems encountered previously in obtaining satisfactory antigens. By further modifications of the procedure, it has been possible to standardize and compare tuberculins serologically, and to demonstrate quantitative and qualitative differences between these antigens (4). Nevertheless, sera from tuberculous and nontuberculous humans (including BCG-vaccinated persons) were found to be unsatisfactory for studying these tuberculins due to the variations in their hemagglutinin content. Frequently a serum, especially among those obtained from BCG-vaccinated students, was found in which all of the hemagglutinins could not be completely removed, regardless of the tuberculins used for adsorption. To study the problem of selective adsorption and to attempt to determine the potentialities of this technique in elucidating serologic differences between strains and species of *Mycobacteria*, hemagglutination and hemagglutinin adsorption tests were made on both human and rabbit antisera against homologous and heterologous tuberculins.

METHODS AND MATERIALS

The methods for preparing sheep erythrocytes, antigens, and test sera for the hemagglutination test were identical with those described by Rothbard, Dooneief, and Hite (3). Old tuberculins were prepared by the method outlined by the Bureau of Animal Industries from cultures of *Mycobacterium butyricum* and *M. tuberculosis* strains BCG, H37Ra, H37Rv, and strains 324, 350, and 9077, freshly isolated from active cases of tuberculosis. Occasionally, a sample of commercial purified protein derivative (PPD) was included in the tests for comparative purposes.

Antisera were obtained from rabbits inoculated either subcutaneoulsy or intravenously with 1 ml. of a young living culture (Dubos medium) of each of the above seven cultures. All rabbits were bled from the heart six weeks after injection; the sera were separated and frozen until studied. The hemagglutination titers of the antisera varied between 1:32 and 1:64 when tested against tuberculins standardized to the equivalent strength of Lederle 4X tuberculin.

The modified hemagglutination test and the hemagglutinin adsorption technique were carried out by the methods previously described (4). Whereas two adsorptions were sufficient to remove the homologous hemagglutinins from human sera, at least three adsorptions were necessary to remove the homologous hemagglutinins from rabbit antisera and, occasionally, four or five adsorptions were necessary.

[1] From the Department of Bacteriology, Hahnemann Medical College, Philadelphia, Pennsylvania.

RESULTS

Antisera prepared in rabbits against the various strains of *Mycobacteria* were found to contain hemagglutinins against both the homologous and heterologous tuberculins as demonstrated by cross-hemagglutination tests. The sera and antigen titers are shown in tables 1 and 2, respectively, indicating the response

TABLE 1

HOMOLOGOUS AND HETEROLOGOUS HEMAGGLUTINATION TITERS* OF RABBIT ANTISERA

RABBIT ANTISERUM	AGGLUTINATING TUBERCULINS					
	M. butyricum	BCG	H37Ra	H37Rv	350	324
M. butyricum	1:64†	1:32	1:32	1:32	1:8	1:8
BCG	1:64	1:128	1:64	1:32	1:16	1:16
H37Ra	1:32	1:8	1:32	1:32	1:16	1:16
H37Rv	1:8	1:16	1:16	1:32	1:16	1:16
350	1:32	1:16	1:64	1:64	1:64	1:64
324	1:32	1:32	1:64	1:64	1:64	1:64

* Methods used were identical with those described by Rothbard, Dooneief, and Hite (3).

† Highest dilution of serum agglutinating sheep erythrocytes sensitized with 300 to 400 mg. of Old Tuberculin per ml. (equivalent to a 1:12 dilution of Lederle 4X tuberculin).

TABLE 2

HOMOLOGOUS AND HETEROLOGOUS ANTIGEN TITERS OF RABBIT ANTISERA

RABBIT ANTISERA	AGGLUTINATING TUBERCULINS					
	M. butyricum	BCG	H37Ra	H37Rv	350	324
M. butyricum	1:1,000,000*	1:1,000	1:10,000	1:5,000	1:2,000	1:2,000
BCG	1:100,000	1:10,000	1:10,000	1:5,000	1:2,000	1:2,000
H37Ra	1:1,000,000	1:1,000	1:10,000	1:5,000	1:1,000	1:2,000
H37Rv	1:1,000,000	1:1,000	1:5,000	1:10,000	1:4,000	1:4,000
350	1:10,000	1:1,000	1:10,000	1:5,000	1:4,000	1:4,000
324	1:10,000	1:1,000	1:10,000	1:5,000	1:4,000	1:4,000

* Highest dilution of tuberculin which can be used to sensitize sheep erythrocytes for agglutination in the presence of a 1:8 dilution of the rabbit antisera.

obtained with both techniques. Antigenic differences were not apparent by either of these techniques and could be demonstrated only by hemagglutinin adsorption experiments.

The results of the hemagglutinin adsorption experiments are shown in table 3. Purified protein derivative (PPD) and tuberculin prepared from the pathogenic strain 9077 were included in this series of tests as adsorbing antigens for comparative purposes. The data are expressed as the per cent of hemagglutinins adsorbed from the sera calculated from the reduction in antigen titer. Although these results have been repeatedly confirmed in this laboratory, only obvious

TABLE 3

THE SELECTIVE ADSORPTION OF HEMAGGLUTININS FROM RABBIT ANTISERUM BY HOMOLOGOUS AND HETEROLOGOUS ANTIGENS (OT AND PPD)

RABBIT ANTISERUM	ADSORBING TUBERCULINS	AGGLUTINATING TUBERCULINS					
		M. butyricum	BCG	H37Ra	H37Rv	350	324
M. butyricum	*M. butyricum*	100*	100	100	100	75	75
	BCG	100	100	100	50	0	0
	H37Ra	95	100	100	100	90	90
	H37Rv	90	99	100	100	100	100
	350	90	90	100	100	100	100
	324	90	99.99	100	100	100	100
	9077	90	100	100	100	100	100
	PPD	99	99.99	100	100	100	100
BCG	*M. butyricum*	100	100	50	80	75	75
	BCG	99.99	100	99	80	75	90
	H37Ra	90	0	100	100	60	80
	H37Rv	80	0	100	100	80	80
	350	90	0	99.99	99.99	100	100
	324	90	50	99.99	99.99	100	100
	9077	100	90	100	100	100	100
	PPD	99.99	99.99	100	100	100	100
H37Ra	*M. butyricum*	100	99.99	99.99	99.99	75	75
	BCG	100	100	99.99	99.99	99	99
	H37Ra	100	100	100	100	100	100
	H37Rv	100	100	100	100	100	100
	350	99.99	99.99	90	100	100	100
	324	99.99	99.99	95	100	100	100
	9077	99.99	100	50	100	100	100
	PPD	99.99	99.99	99.99	100	100	100
H37Rv	*M. butyricum*	100	99.99	100	50	50	50
	BCG	100	100	99.99	50	75	75
	H37Ra	100	100	100	100	50	50
	H37Rv	100	100	100	100	100	100
	350	90	75	99.99	99	100	100
	324	90	99.99	99.99	99	100	100
	9077	100	100	99.99	50	100	100
	PPD	99.99	99.99	100	99.99	100	100
M. tuberculosis 350	*M. butyricum*	100	99.99	99.99	99.99	50	50
	BCG	90	100	99.99	99.99	50	75
	H37Ra	100	0	100	100	99	99
	H37Rv	99	0	100	100	100	100
	350	100	100	100	100	100	100
	324	99.99	0	99	100	100	100
	9077	100	100	99	80	100	100
	PPD	99	99.99	100	100	75	100
M. tuberculosis 324	*M. butyricum*	100	100	100	100	75	75
	BCG	99.99	100	100	100	75	75
	H37Ra	100	90	100	100	100	99
	H37Rv	99.99	90	100	100	100	100
	350	100	0	100	100	100	100
	324	100	100	100	100	100	100
	9077	100	100	99.99	50	100	100
	PPD	99.99	99.99	100	100	100	99.99

* Per cent of hemagglutinins adsorbed as calculated from the reduction in antigen titers—antiserum held at a constant 1:8 dilution. The significance of 99.99 per cent hemagglutinin adsorption is not known and is noted merely to indicate that erythrocytes sensitized with high concentration of antigen were agglutinated in the antisera.

facts are noted to avoid any errors which may result from attempting to arrive at any definite conclusions at this phase of the work. The following facts, however, are evident:

(*1*) The freshly isolated pathogenic strains of *Mycobacteria* studied appear to be antigenically similar except in a few instances; (*2*) the strain of H37Rv (last guinea pig passage approximately twenty-four months ago) used in this laboratory is not antigenically typical of freshly isolated strains; (*3*) the antigenic relationship between the H37Ra and H37Rv strains is obvious; (*4*) these results confirm previous observations of the antigenic difference between the pathogenic and nonpathogenic strains; (*5*) purified protein derivative (PPD) when used as an adsorbing antigen does not remove all of the homologous hemagglutinins from the antisera. Neither does it completely remove the hemagglutinins against the tuberculins prepared from *M. butyricum* and BCG from any of the rabbit antisera; (*6*) the irregularities observed with some of the adsorbed sera from BCG-vaccinated students were also evident with the adsorbed rabbit sera.

These irregularities noted with the adsorbed sera from BCG-vaccinated persons could possibly be due to one of two factors. One, BCG may dissociate antigenically when injected into man or animals, as shown by the fact that the homologous antigen will not remove all of the heterologous hemagglutinins from BCG sera. Second, BCG, a bovine strain, may have a somewhat different antigenic pattern from those of the human or saprophytic strains, as shown by the fact that in several instances tuberculins prepared from human strains 350 and 324 failed to remove any of the hemagglutinins against BCG from rabbit antisera. The former hypothesis is favored, however, for it is known that BCG does dissociate *in vitro* (5).

The Specificity of the Hemagglutinin Adsorption Technique

As may be seen from the data in table 3, tuberculins prepared from nonpathogenic *Mycobacteria*, i.e., BCG, H37Ra, and *M. butyricum*, are not effective in adsorbing all of the hemagglutinins from tuberculous human and rabbit sera, whereas they were effective in removing the hemagglutinins from the sera of nontuberculous humans and from the sera of rabbits which had been injected with nonpathogenic strains. This observation formulated the hypothesis that, if sera from tuberculous and nontuberculous persons were adsorbed with sheep erythrocytes sensitized with tuberculin prepared from nonpathogenic strains and the adsorbed sera were subsequently tested by the modified hemagglutination test (serum constant-antigen diluted) with an antigen prepared from pathogenic tubercle bacilli, the differential in the antigen titers should be significant. In attempting to circumvent the anticipated nonadsorpability of the hemagglutinins from sera of BCG-vaccinated students, it was decided to adsorb all sera with both H37Ra and BCG tuberculins. (H37Ra tuberculin was chosen after several preliminary experiments were carried out.) The hemagglutinin adsorption technique was identical with that previously described. Four adsorptions were routinely carried out, two with H37Ra and two with BCG tuber-

culin-sensitized erythrocytes. As may be seen in table 3, the tuberculin used to sensitize the agglutinating erythrocytes should be prepared from a pathogenic strain. For this purpose, tuberculin prepared from strain 350 was used throughout these experiments, although tuberculins prepared from the other pathogenic strains tested were just as satisfactory.

The hemagglutination titers of all sera were routinely determined by the method described by Rothbard, Dooneief, and Hite (3). Sera with a titer of less than 1:2 were recorded as negative. Occasionally a serum from a known tuberculous patient gave a negative hemagglutination test, but as a rule these

TABLE 4

THE RESULTS OF THE MODIFIED HEMAGGLUTINATION TEST DEMONSTRATING THE ADSORPTION OF HEMAGGLUTININS FROM REPRESENTATIVE SAMPLES OF SERA WITH BCG- AND H37RA-SENSITIZED SHEEP ERYTHROCYTES

TYPE OF HUMAN SERA	SERA HEMAGGLUTINATION TITER	SERUM DILUTION USED IN TEST	DILUTIONS OF 350 TUBERCULIN USED TO SENSITIZE THE AGGLUTINATING SHEEP ERYTHROCYTES						
			1:10	1:20	1:40	1:80	1:160	1:320	1:640
Tuberculous	1:32	1:16	+	+	+	+	+	−	−
		1:32	+	+	+	−	−	−	−
		1:64	+	+	−	−	−	−	−
Tuberculous	1:16	1:8	+	+	+	+	−	−	−
		1:16	+	+	+	−	−	−	−
		1:32	+	−	−	−	−	−	−
Nontuberculous	1:32	1:16	+	−	−	−	−	−	−
		1:32	−	−	−	−	−	−	−
		1:64	−	−	−	−	−	−	−
BCG-vaccinated	1:16	1:8	+	+	+	+	+	+	+
		1:16	+	+	+	+	+	−	−
		1:32	+	+	−	−	−	−	−
BCG-vaccinated	1:16	1:8	−	−	−	−	−	−	−
		1:16	−	−	−	−	−	−	−
		1:32	−	−	−	−	−	−	−
Leprous	1:256	1:128	−	−	−	−	−	−	−
		1:256	−	−	−	−	−	−	−
		1:512	−	−	−	−	−	−	−

sera were from patients with far advanced tuberculosis who were receiving drug therapy. However, a sufficient number of sera have not been tested to place any significance on this observation. All sera which gave hemagglutination titers were adsorbed undiluted and were retested by the modified antigen-dilution technique. Three series of tubes were set up for each serum adsorbed. To one series was added the adsorbed serum diluted to its original hemagglutination titer; one series received one-half of the concentration; and the third series, a concentration twice that of the original titer. Sheep erythrocytes sensitized with decreasing concentrations (1:10 to 1:640) of 350 tuberculin were added to each series of tubes. All tubes were incubated and read in the usual manner. Appropriate controls were included with each serum.

The results shown in table 4 illustrate the type of response obtained with representative samples of serum, while the results in table 5 summarize the data from all of the sera tested by this method to date. These results indicate that it is possible to adsorb hemagglutinins selectively from the serum of nontuberculous and non-BCG-vaccinated persons except in a relatively few instances. Approximately 20 to 25 per cent of the BCG-vaccinated student sera adsorbed retained sufficient hemagglutinins to be indistinguishable from tuberculous sera.

TABLE 5

RESULTS OF THE MODIFIED HEMAGGLUTINATION PROCEDURE DEMONSTRATING THE SPECIFICITY OF THE TEST

SOURCE OF SERUM	TOTAL NUMBER OF SERA TESTED	NUMBER OF SERA GIVING A POSITIVE HEMAGGLUTINATION TEST	RANGE OF HEMAGGLUTINATION TITERS	NUMBER OF SERA IN WHICH ANTIBODIES WERE STILL DEMONSTRATED AFTER ADSORPTION
Tuberculous patients	68	60*	1:8–1:128	59†
Apparently nontuberculous patients	174	37	1:4–1:32	2‡
BCG-vaccinated students	17	15	1:4–1:32	4
Leprous patients	3	3	1:64–1:256	0

* The eight sera from tuberculous patients failing to give a positive hemagglutination test were from far advanced patients receiving treatment.

† The hemagglutinins were removed from the serum of one patient with far advanced tuberculosis receiving streptomycin and PAS when adsorbed with the tuberculins of H37Ra and BCG.

‡ From clinic patients with positive serologic tests for syphilis and normal chest roentgenograms.

Although these results are based on only 115 positive hemagglutinating sera, the specificity is encouraging.

DISCUSSION

The data presented in this paper indicate that hemagglutinins can be selectively adsorbed from human sera and from the sera of rabbits inoculated with various species of *Mycobacteria*. Emphasis is placed on the fact, however, that these results represent only a small part of the problem, and the cultures used are few in number and may not necessarily be typical of the species represented. The writers appreciate and respect the complexity of this problem and have therefore refrained from speculation on many of the interesting results obtained. The value of this type of procedure in studying tuberculous antigens, however, is evident, as shown by the consistency and the specificity of results.

Irrespective of the possibility that the cultures studied were not necessarily typical of the species, the data warrant a brief discussion of the antigenic differences found. It would appear from these results that the pathogenic and nonpathogenic species can be distinguished antigenically although both species contain common antigens. It would be impossible at this time to comment on

the antigenic differences between the nonpathogenic members of the genus, with the exception of the BCG culture studied, in which case there were demonstrable antigenic differences. In general, the results indicate that the members of the nonpathogenic group are antigenically related; however, there are apparently a few minor differences. This same generalization can be made regarding the members of the pathogenic group. One chromogenic strain of questionable pathogenicity isolated from the sputum of a patient suspected of being tuberculous was studied by this technique to determine if it belonged to the pathogenic or nonpathogenic group. The results obtained (not included in the tables) indicated that it was more closely related to the nonpathogens. Subsequent histologic sections of guinea pigs inoculated with this culture confirmed this finding.

The sera obtained from three leprous patients contained hemagglutinins that adsorbed in a manner similar to those in sera from nontuberculous patients.

SUMMARY

A hemagglutinin adsorption technique has been described which will permit the selective adsorption of tuberculin hemagglutinins from rabbit and human antisera. Although the results presented were obtained from a study of only seven microbial species, the following observations were consistent.

There are antigenic differences between tuberculins prepared from pathogenic and nonpathogenic strains of *Mycobacteria*, although common antigens are present in both groups.

Strains within these two groups appear to be closely related antigenically with the exception of minor differences. The importance of these differences was not determined.

Antigenic differences and similarities between H37Ra and H37Rv are apparent.

The hemagglutinin-adsorption technique has been shown to have a high degree of specificity.

SUMARIO

La Especificidad de la Técnica de Absorción de Hemaglutininas en el Estudio Serológico de la Tuberculosis

La técnica descrita para la absorción de hemaglutininas permite la absorción selectiva de hemaglutininas tuberculínicas en los antisueros cuniculares y humanos. Aunque los resultados presentados proceden del estudio de no más de siete especies, las siguientes observaciones fueron constantes.

Hubo diferencias antigénicas entre las tuberculinas preparadas de cepas patógenas y anapatógenas de *Mycobacteria*, aunque en ambos grupos, había antígenos en mancomún.

Las cepas pertenecientes a esos dos grupos parecen ser íntimamente afines antigénicamente, exceptuadas pequeñas diferencias. No se determinó la importancia de dichas diferencias.

Eran manifiestas las diferencias y semejanzas antigénicas entre H37Ra y H37Rv.

Queda demostrado que la técnica de absorción de hemaglutininas posee elevada especificidad.

RESUME

La spécificité de la technique d'absorption des hémagglutinines dans l'étude sérologique de la tuberculose

Une technique d'absorption de l'hémagglutinine a été décrite; elle permet l'absorption spécifique des hémagglutinines de la tuberculine d'antisérums d'homme et de lapin. Bien que les résultats présentés aient été obtenus d'après l'étude de sept espèces seulement, les observations suivantes ont été constantes:

Il existait des différences antigéniques entre les tuberculines préparées à partir de souches pathogènes de *Mycobacteria*, en dépit de la présence d'antigènes communs dans les deux groupes.

Les souches composant ces deux groupes semblent être étroitement apparentées du point de vue antigénique, à quelques différences mineures près. L'importance de ces différences n'a pas été déterminée.

Les différences et les ressemblances entre H37Ra et H37Rv sont apparentes.

Il a été démontré que la technique de l'absorption des hémagglutinines possédait un haut degré de spécificité.

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Notes

TUBERCULIN PATCH TEST SURVEY AMONG SCHOOL-AGE CHILDREN IN LIBERIA

No accurate answer can be given to inquiries on the incidence, prevalence, or mortality rates due to infections with *M. tuberculosis* in Liberia. This is, in a large measure, due to the fact that except for the capital, Monrovia, reporting of causes of illnesses and of deaths are incomplete.

In order to acquire some specific data on the prevalence of tuberculosis infection in Liberia, the United States Public Health Mission in Liberia began a case-finding project in 1947, using the tuberculin patch test[1] for the initial screening. The positive reactors were followed by chest roentgenograms and those revealing suspicious or definite roentgenographic evidence of pulmonary tuberculosis were further studied by a more detailed medical examination, including study of the sputum for *M. tuberculosis*. Acid-fast staining of fresh sputum, guinea pig inoculations and culture, using Petroff's medium, were made of specimens from all persons suspected of having tuberculosis.

By July 1, 1950, tuberculin patch tests had been done on 10,419 Liberians scattered over the country, but mostly along the Atlantic coast where they were more easily reached by boat or jeep. Of the 10,419 persons tested, 804, or 8 per cent, gave positive reactions. The 10,419 persons tested consisted of the following:

School-age children—8,551, equivalent to 82 per cent of the total.

Adults—1,868, equivalent to 18 per cent of the total.

The test was made by applying the patch to the chest or back of the person after cleaning the skin with ether or acetone. The patches were removed after forty-eight hours and all patch sites which showed 1 cm. or more of easily palpable edema in the tuberculin impregnated area and not in the area of the controlled substance were read as positive. When both the tuberculin impregnated area and the control area showed strong reaction, the result was recorded as suspicious and further examinations were done. When neither the tuberculin impregnated area nor the control area of the patch showed easily palpable edema or inflammation, the reaction was considered negative.

Since the tuberculin patch test shows its greatest case-finding usefulness in children, the survey was confined almost exclusively to the estimated age group of 5 to 25 years, as representing the school-age group. The findings in the tables 1, 2, and 3 may be used as a baseline for future comparative studies on changes in prevalence of tuberculosis in the various areas.

Except for the Central Province, the rural areas were all within 40 miles of the Atlantic coast.

It is interesting to observe that the Lott Carey Mission and Gola Forest groups, both rural groups in the Western Province with very little contact with the coastal cities prior to 1946, have a significantly lower percentage of positive reactors. The percentage of positive reactors in the rural areas of this province is only half that of Monrovia, the capital city and chief seaport, only 30 miles away.

Mention should be made about the relatively high percentages at the Bromley Mission and the Central Province groups. The former represents a group of late adolescent girls who come chiefly from families inhabiting the coastal cities, and who spend most of their

[1] Tuberculin patch test (Vollmer). Material was supplied by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

TABLE 1

RESULTS OF TUBERCULIN PATCH TESTS ON SCHOOL-AGE GROUP (5 TO 25 YEARS) IN LIBERIA, 1947–1950

SCHOOL	NUMBER TESTED	NUMBER POSITIVE	PERCENTAGE POSITIVE
Monrovia*	3,415	340	10
Marshall*	145	15	10
Bassa*	1,001	83	8
Sinoe*	1,235	71	6
Monrovia†	959	68	7
Lott Carey Mission†	145	7	5
Bromley Mission	102	12	12
Central Province	1,316	128	10
Gola Forest	233	12	5
Total	8,551	736	9

* City.
† Rural areas.

TABLE 2

RESULTS OF TUBERCULIN PATCH TESTS ON ADULTS IN CERTAIN AREAS IN LIBERIA, 1947–1950

AREA	NUMBER TESTED	NUMBER POSITIVE	PERCENTAGE POSITIVE
Miscellaneous	799	41	5
Central Province (lower)	65	6	9
Central Province (upper)	700	13	2
Teachers' Institute	304	8	3
Total	1,868	68	4

TABLE 3

RESULTS OF TUBERCULIN PATCH TESTS ON SCHOOL-AGE CHILDREN IN LIBERIA, 1947–1950

AGE GRADE RANGE	NUMBER TESTED	NUMBER POSITIVE	PERCENTAGE POSITIVE
5 to 9 years; kindergarden through fourth grade	6,410	536	8
10 to 14 years; fifth grade to completion of elementary school	1,578	143	9
15 to 20 years; high school	442	49	11
20 to 25 years; college	121	8	7
Total	8,551	736	9

vacations between school sessions in these cities with relatives. The rural towns and villages covered in the Central Province group are along the main inland highway, especially around the town of Ganta, where most of the inland traffic and trade between French Guinea of West Africa and Liberia converge.

Most of the adults tested here are residents of the hinterland. The Teachers' Institute group comprises teachers from all parts of Montserrado County. They come to Monrovia once yearly for a refresher course in teaching methods. The fact that only 3 per cent of this small group of adult teachers gave positive reactions is gratifying. None of the 8 positive reactors among the teachers showed any evidence of active disease on chest roentgenograms. Among the other 60 adult positive reactors, only 4 were shown to have active chest disease. This represents a ratio of approximately 2 active cases per 1,000 adults. The apparent explanation for this low prevalence in adults is probably due to the fact that a large percentage of them were teachers or working around the schools. The teachers and others working in the field of education or religion are generally from the higher economic brackets, where better housing, less overcrowding, better food, and better medical care would make them less exposed to infections than the poor and less intelligent groups.

The distribution in table 3 is fairly characteristic of the enrollment distribution in the schools in the coastal areas of Liberia. These figures show that only approximately 7 per cent of the school children go above the elementary school level. The probable explanation of the lower percentage of positive reactors among the college group is that they come from the highest economic brackets and are less subject to diseases such as tuberculosis, which is associated with poverty.

The names of the positive reactors from each school were sent to the principal thereof and the teaching supervisor of the district with a request that the positive reactors be sent to the X-ray Section of the United States Public Health Mission in Liberia for chest plates. Up to July 1, 1950, 327, or 44 per cent, of the positive reactors among the age group 5 to 25 years had received roentgenographic and clinical examinations. The roentgenograms were taken by Assistant Sanitarian (R) Romey W. Keys. The films were interpreted and the clinical examinations, including additional laboratory examinations when indicated, were performed by the present writer.

Fifteen of the 327 persons examined roentgenographically showed some type of intrathoracic disease. All those with suspicion of chest disease, those who gave medical histories of tuberculosis in the families, and those who presented other medical evidences of probable tuberculosis were given further examinations which included Ziehl-Neelsen acid-fast staining of sputum and guinea pig inoculations. From these added examinations, 3 persons were found with active tuberculosis of the lung in its infectious stage; thus, the estimated prevalence was less than 4 active cases per 10,000 students. These children and their parents were given the best practical instructions for home management since complete isolation was not practicable in Liberia at the time.

These findings indicate that tuberculosis was not among the major health hazards of the Republic in 1947. Bone-joint and lymphatic tuberculosis are seen in the ratio of approximately one case in 30,000 clinic admissions in Monrovia.

Dairying and drinking of milk are not yet a part of Liberian life. In spite of the apparent low prevalence, preventive measures should be started now. In contrast to the low prevalence found in adults during the survey which began in 1947, a check in 1952 on clinical cases coming from the same areas where only 4 cases were found in 1947 showed 45 known cases of active tuberculosis in adults. The chief factors responsible for this increase are the marked increase in industrialization of the areas, with influx of labor from several areas in Liberia and adjacent colonies. With this influx have come much over-crowding of the huts, more beer houses, dance halls, and other means of overcrowded indoor recreations, as well as a change in the sleeping pattern of the indigenous groups. Instead of going to bed as soon as dark comes, as was customary, they now stay up at

these recreational places until all hours of the night and try to do a full day's work in the mines, docks, and on road-building projects.

In summary: In Liberia, 8,551 children of school age were given Vollmer tuberculin patch tests. Seven hundred and thirty-six gave positive reactions, which comprises 9 per cent of the group. Three hundred and twenty-seven of the positive reactors were given further medical examinations, including roentgenograms of the chest. Of these, 15 gave some evidence of intrathoracic disease. Further examination of these 15 persons who showed roentgenographic and clinical evidences of probable tuberculosis revealed 3 active cases of pulmonary tuberculosis among the 8,551 students given tuberculin patch tests.

One thousand eight hundred and sixty-eight adults were given tuberculin patch tests, of whom 68 (4 per cent) gave positive reactions. There were 4 active cases among these adults, with an estimated prevalence of 2 per 1,000.

In comparison with some of the other tropical diseases, tuberculosis in 1947 was not among the major health hazards of Liberia, but by 1952 a threat had developed which is believed to reflect a defect in readiness to take care of the problem of overcrowding and community equilibrium associated with the recent rapid industrialization of certain areas of the republic.

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United States Public Health Mission
Liberia

Hildrus A. Poindexter

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RESPIRATORY QUOTIENTS OF TUBERCLE BACILLI AT LOW OXYGEN TENSION

Novy and Soule[1] found no change in the respiratory quotient (R.Q.) of tubercle bacilli growing at low oxygen tension, while Kempner[2] reported a similar finding with resting tubercle bacilli. In the course of a study on the respiration of tubercle bacilli, the present

TABLE 1

RESPIRATORY QUOTIENTS* OF TUBERCLE BACILLI IN AIR AND AT 1 PER CENT OXYGEN TENSION

STRAIN	ENDOGENOUS		IN LACTATE		IN DUBOS-DAVIS MEDIUM	
	Air	1 per cent O_2	Air	1 per cent O_2	Air	1 per cent O_2
H37Ra	0.93	0.99	0.97	1.02	0.77	0.97
H37Rv	0.91	0.98	0.97	1.08	0.74	0.85
JH6Ra	1.00	1.86	0.83	1.33	0.80	0.84
JH16Ra	1.04	1.24	0.65	0.93	0.83	0.86
BCG	0.83	0.92	0.86	0.94	0.84	0.91
Campbell	1.63	1.90	0.90	1.50	0.81	0.83
Cutter	1.08	1.29	0.89	1.00	0.79	0.83
Ravenel	0.80	0.88	0.88	0.93	0.83	0.92

* Determined during a sixty-minute period at 37°C.; endogenous and in lactate (0.45 per cent v/v lactic acid) in M/15 phosphate buffer of pH 6.2.

TABLE 2

CHANGE WITH TIME OF RESPIRATORY QUOTIENTS* OF TUBERCLE BACILLI IN AIR AND AT 1 PER CENT OXYGEN TENSION

STRAIN	TIME	ENDOGENOUS		IN LACTATE		IN DUBOS-DAVIS MEDIUM	
		Air	1 per cent O_2	Air	1 per cent O_2	Air	1 per cent O_2
H37Ra	First hour	0.93	0.99	0.97	1.02	0.78	0.88
	Second hour	0.91	1.04	0.97	1.11	0.93	1.00
	Third hour	0.90	1.33	1.02	1.52	0.89	0.98
H37Rv	First hour	0.91	0.98	0.97	1.08	0.75	0.90
	Second hour	0.89	0.98	1.00	1.12	0.79	0.97
	Third hour	0.85	1.30	1.17	1.66	0.82	0.97

* Determined at 37°C.; endogenous and in lactate (0.45 per cent v/v lactic acid) in M/15 phosphate buffer of pH 6.2.

writer obtained unambiguous data indicating an increase in the R.Q. at low oxygen tensions. Ten common strains of *Mycobacterium tuberculosis*, cultivated in Dubos-Davis medium,[3] and the conventional two-vessel Warburg technique with corrections for carbon dioxide retention were employed. The results are presented in table 1. As further

[1] NOVY, F. G., AND SOULE, M. H.; J. Infect. Dis., 1925, *36*, 168.

[2] KEMPNER, W.; Am. Rev. Tuberc., 1939, *40*, 157.

[3] DUBOS, R. J., AND DAVIS, B. D.; J. Exper. Med., 1946, *83*, 409.

evidence for an increase in the R.Q. at low oxygen tensions, the data in table 2 represent respiratory quotients of two strains of tubercle bacilli during a three-hour period. At the end of this time respiration was negligible, indicating that the gas tension had diminished to considerably less than the starting 1 per cent O_2 (delivered from a commercial mixture containing 1 per cent O_2, 98.97 per cent N_2, and 0.03 per cent CO_2).

There is a strong prevailing opinion against the presence of fermentations in tubercle bacilli (cf. review of Edson[4]). However, these results suggest that at least an endogenous fermentative metabolism can occur. It is uncertain whether this tendency for the R.Q. to increase at low O_2 tensions in the presence of lactate is endogenous or exogenous in origin.

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February 24, 1953

[4] Edson, N. L.; Bact. Rev., 1951, *15*, 147.

INEFFECTIVENESS OF ISONIAZID AND IPRONIAZID IN THERAPY OF SARCOIDOSIS[1]

The effectiveness of isonicotinic acid hydrazides in the treatment of tuberculosis has been established. It appeared that a trial of these drugs in sarcoidosis would indicate whether their therapeutic activity was limited to tuberculosis or extended to a disease which exhibits certain histologic resemblances to tuberculosis but which is considered by most investigators not of tuberculous etiology.

Marked improvement and even complete clearing of sarcoid lesions may occur without treatment over an interval of months. For this reason, it was believed that a prompt response similar to that noted with cortisone[2, 3] should be required as evidence of therapeutic activity. Nine representative patients exhibiting a variety of manifestations, including pulmonary, mediastinal, cutaneous, parotid, osseous, hepatic, and splenic involvement, have been treated. Six patients received isoniazid,[4] 2 received iproniazid,[4] and one received courses of both drugs. The results, as indicated in table 1, were not impressive. Slight to moderate improvement in appetite was noted in 5 patients with significant weight gain in 2 instances. Definite improvement of pulmonary lesions was noted in only one patient, in the second month of treatment, and may have been coincidental. Two patients showed progression of disease while on therapy. Detailed respiratory function studies were carried out by Dr. H. L. Motley[5] in one patient and these revealed no change as the result of treatment. That the lesions were susceptible to drug therapy was demonstrated in 2 patients, who, after failing to respond to isoniazid medication, were given cortisone:

> J. E., a 25-year-old Negro female, was admitted to Graduate Hospital on April 10, 1952, with erythema nodosum. Roentgenographic examination of the chest revealed marked hilar adenopathy, and slight parotid enlargement was noted. Gastrocnemius muscle biopsy revealed characteristic lesions of sarcoidosis. Isoniazid was started on April 22. Parotid swelling became progressively more marked, and painful nodules continued to appear on the legs. Isoniazid was discontinued on April 30 and cortisone therapy was instituted in dosage of 100 mg. daily. The parotid enlargement disappeared in forty-eight hours and the erythema nodosum faded. Cortisone was stopped on May 26, after a total of 2.6 gm. had been given. The hilar nodes were not altered in size; there has been no recurrence of parotid enlargement or erythema nodosum.
>
> J. W., a 32-year-old Negro male, was admitted to Graduate Hospital on April 10, 1952, because of a papular rash on the face of four months' duration. Biopsies of skin and an axillary lymph node showed characteristic lesions of sarcoidosis. Roentgenographic examination of the chest revealed no abnormalities. Isoniazid was given from April 12 to May 4, without evident improvement in the cutaneous lesions. Cortisone was started in dosage of 100 mg. daily on May 4; marked improvement was noted within a week. Therapy was discontinued on July 10, at which

[1] This investigation was supported by a medical research grant from the National Institutes of Health, Public Health Service.

[2] Sones, M., Israel, H. L., Dratman, M. B., and Frank, J. H.: New England J. Med., 1951, *244*, 209.

[3] Siltzbach, L. E.: Am. J. Med., 1952, *12*, 139.

[4] Supplied as Rimifon and Marsilid, respectively, by Hoffmann-La Roche, Inc., Nutley, New Jersey, through the kindness of Dr. Leo Pirk.

[5] Jefferson Medical College, Philadelphia, Pennsylvania.

TABLE 1

RESULTS OF ISONIAZID AND IPRONIAZID IN NINE PATIENTS WITH SARCOIDOSIS

PATIENT	TYPE	DURATION OF TREATMENT	DAILY DOSAGE	RESULTS
H. F., M-N-40	Generalized, chronic	3/7 to 4/6	Isoniazid, 250 mg.	No objective change; weight gain of 7 pounds
J. W., M-N-32	Skin, lymph nodes; acute	4/12 to 5/4	Isoniazid, 300 mg.	No improvement
		7/28 to 9/5	Iproniazid, 300 mg.	No improvement
J. E., F-N-25	Erythema nodosum, hilar lymph nodes, parotids; acute	4/22 to 4/30	Isoniazid, 250 mg.	Marked progression of parotid enlargement
A. S., M-W-33	Lungs; chronic	3/17 to 6/2	Isoniazid, 300 mg.	Appetite increased; no weight gain; slight roentgenographic improvement
J. C., M-W-22	Lungs; acute	3/20 to 4/21	Isoniazid, 300 mg.	No subjective or objective change
M. C., F-N-27	Lungs; acute	3/10 to 6/9	Isoniazid, 250 mg.	No change
E. H., F-N-28	Lungs; chronic	4/9 to 7/8	Isoniazid, 200 mg.	Slight symptomatic improvement; roentgenograms and respiratory function studies unimproved
E. W., F-N-40	Lungs, parotids, liver, spleen; chronic	4/30 to 8/8	Iproniazid, 200 mg.	Slight symptomatic improvement; pulmonary lesions slightly worse
H. M., F-N-31	Lungs, liver, lymph nodes; chronic	7/18 to 9/15	Iproniazid, 250 mg.	Symptomatic improvement; gained 15 pounds; moderate roentgenographic improvement in second month

time the cutaneous lesions were no longer discernible. The lesions recurred and iproniazid was given from July 28 to September 5, without apparent effect.

In summary: A trial of isoniazid or iproniazid therapy has been made in patients with sarcoidosis. Nine patients with a variety of lesions were studied. Slight to moderate symptomatic improvement was noted in 5 instances, with roentgenographic improvement in one of these patients. Progression of disease occurred in 2 patients during therapy.

Reversibility of the lesions was demonstrated in 2 instances in which, after failure of antimicrobial treatment, prompt response to cortisone was observed. Since improvement of the frequency and degree noted during the administration of the isoniazid and iproniazid is commonly observed in untreated patients, it is concluded that the therapeutic activity of these drugs does not extend to sarcoidosis.

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October 10, 1952

PRELIMINARY NOTE ON THE EFFECT OF ISONIAZID AND IPRONIAZID IN MURINE LEPROSY

Isoniazid and iproniazid were studied in experimental murine leprosy using the short-term method in white mice as described by Grunberg and Schnitzer.[1] This method consisted of an intraperitoneal injection of 0.5 cc. of the supernatant of a 10^{-1} diluted suspension of a ground rat leproma. Treatment was instituted immediately after infection and continued for a total of twenty-eight days. The animals were allowed, with isoniazid and iproniazid, to feed on the medicated diet ad libitum and, with Promin, which was used as a reference standard, were given single daily injections subcutaneously. All mice were sacrificed on the twenty-ninth day, the lesions were removed from the peritoneum, crushed between two slides, and the number of organisms per slide was estimated using the symbol 3.0 to designate innumerable organisms in each microscopic field.

TABLE 1

THE CHEMOTHERAPEUTIC ACTIVITY OF ISONIAZID AND IPRONIAZID AGAINST THE INTRAPERITONEAL INFECTION OF WHITE MICE WITH M. LEPRAEMURIUM

Infection: 0.5 cc. of a 10^{-1} dilution of a rat leproma
Treatment: 28 days
Autopsy: twenty-ninth day

COMPOUND	DOSE	NUMBER OF ANIMALS	ESTIMATE OF ORGANISMS OBSERVED IN LESIONS
	mg/kg/day		
Isoniazid	500 Diet	21	0.86
Isoniazid	250 Diet	31	0.57
Iproniazid	500 Diet	14	0.66
Iproniazid	250 Diet	8	0.59
Promin	500 Subcutaneous	31	1.05
Controls 1*	—	11	0.23
Controls 2†	—	25	2.2

* Inoculum boiled at 100°C. for five minutes
† Live bacteria

In evaluating compounds by this method, it should be emphasized that, since the results are based on the estimate of organisms in the lesions, they can only be of approximate quantitative significance. The results of the present experiments are given in table 1.

In table 1 it can be seen that the controls injected with live bacteria had a well-developed infection with numerous organisms in the lesions. As compared with the original inoculum, which is represented by the boiled material (controls 1), the number of bacilli of the controls infected with live inoculum had increased approximately ten times during the observation period. Promin exhibited its customary type of activity in good agreement with earlier published results.[1] Both isoniazid and iproniazid seemed to be as active, if not slightly more active, than Promin. Dose for dose, both hydrazine derivatives of isonicotinic acid seemed to be on approximately the same order of activity. However, with each drug, the lower dose of 250 mg. per kg. per day seemed to be somewhat more active than the higher dose of 500 mg. per kg. per day. Therefore, using the *t*-distribution method,

[1] Grunberg, E., and Schnitzer, R. J.: Ann. New York Acad. Sc., 1951, *54*, 107.

the p-value was determined and found to be greater than 0.05 with the doses of isoniazid and greater than 0.5 with iproniazid, thus indicating that these differences were not significant.

In summary: Isoniazid and iproniazid, when tested for their effect against *M. lepraemurium*, were found to exert a marked activity. This activity, although not yet titrated to the end point, seems to be on a lower order than that observed with *M. tuberculosis*.

CHEMOTHERAPY LABORATORIES
HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY

E. GRUNBERG
E. H. TITSWORTH

December 18, 1952

Correspondence

TUBERCULOSIS IN SOUTH AMERICA

To the Editor of The American Review of Tuberculosis:

In the July, 1952, *Bulletin of the International Union Against Tuberculosis*, Dr. O. M. Mistral reported that South America has approximately 150,000 deaths from tuberculosis annually in a population of 100,000,000 and approximately 1,500,000 persons with active tuberculosis, but only about 50,000 beds in tuberculosis institutions. He concluded that it would be "fantastic," "impossible," "utopic," and "unrealistic" to attempt to solve the problem of tuberculosis in South America by building sanatoriums, as it would take a billion dollars merely to build enough to provide the "necessary" one bed per death. He condemned mass roentgenography as "contraindicated" and "nonsensical" in such areas where there are numerous persons known to have tuberculosis who cannot now receive proper care. He urged general social and economic uplift, and propaganda and dispensaries to lessen the spread of infection, especially among contacts and children; and, although he admitted its inadequacy, his strongest recommendation was for massive BCG vaccination to reduce "predisposition" to the disease. Similar sentiments have been repeatedly expressed by other workers.

In the September, 1952, *American Journal of Public Health*, Dr. C. A. Alvarado of Tucuman, Argentina, presents quite a different attitude. Trained personnel, institutional beds, case-finding facilities, early vaccination, public health and tuberculosis education and orientation of the people, and organization for management and supervision, all needed for a control program of prevention, isolation, and treatment, are, he admits, highly lacking. However, he says, "few countries in the world have these six requirements available in the quality and quantity required. . . . If in each highly endemic area we were to wait, before setting up an efficient control system, for a satisfactory level in each of these basic items for the campaign, . . . there would be a delay of . . . years before we could secure progress in the control of tuberculosis." He urges realistic thinking but ambitious planning, with the maximum utilization of all agents and agencies of the area, since "Tuberculosis is first and foremost an infectious disease."

A cursory review of the available literature and casual inquiries on a recent trip around South America suggest, in fact, that the death rates in most South American countries probably never were as high as the impressions derived from the more accessible urban statistics had indicated, and that they have been falling rapidly in most places during the past few years. The number of institutional beds available have also been increasing recently, so that already they approach one bed per thousand population in most parts of South America. Complete care of all persons with active tuberculosis would probably require ten beds per annual death, rather than the old one bed per death goal, but, as Frost has explained, even a few beds may contribute to lower the tuberculosis infection rate. South America has already more beds per population than we have in the United States and a much greater number of beds per death from tuberculosis than we had a generation ago when we had a similar death rate.

Case finding in excess of available institutional facilities, moreover, is the most effective means for stimulating the increase in provision of such beds. Even in the absence of adequate beds, case finding may lead to improved prophylaxis and diminished infection by letting the people themselves know where the danger lies and how to avoid it. Tuber-

culosis in its minimal forms, such as are most apt to be disclosed by mass surveys, are particularly amenable to the recently developed chemotherapeutic agents, even in the absence of institutional care.

In the main railroad station in Rio de Janeiro, all passers-by are invited to have a free X-ray, and a week later receive the completed film and report, with little effort at follow-up. De Abreu maintains that, when people learn that there is something wrong with their chests they usually seek medical aid, and that extensive follow-up and supervision in connection with such diagnoses are unnecessary and bureaucratic. He ascribes much of the recent decline in tuberculosis mortality rates in most places to the extensive fluorographic surveys which are being carried out.

Other workers place greater stress on the improved prognosis in known cases of tuberculosis resulting from recent advances in therapy, especially with streptomycin and para-aminosalicylic acid. Isoniazid and excisional surgery are still too new and too little used to have had any effect on the general tuberculosis mortality rates, and even collapse therapy measures are less often observed than in the United States. Despite the great enthusiasm expressed by proponents of BCG vaccination, both with the "concurrent" oral regimen of De Assis and with the intradermal or percutaneous method sponsored by the UNICEF, these measures, which have been applied to more than a million infants and other young negative tuberculin reactors in South America, have not yet been given to enough of the older adults, who contribute the greater part of the tuberculosis mortality, to be credited with playing any part in the striking reduction in tuberculosis deaths among adults.

OLIVE VIEW SANATORIUM
OLIVE VIEW, CALIFORNIA

Sincerely yours,
EMIL BOGEN

October 27, 1952

REQUEST FOR REPRINTS CONCERNING STRESS AND THE ADAPTIVE HORMONES

To the Editor of The American Review of Tuberculosis:

In perusing the current literature with which this journal is concerned, we note that an ever increasing number of its articles deals with problems pertaining to research on "stress" and the so-called "adaptive hormones" (ACTH, STH, corticoids, adrenergic substances, et cetera).

We are writing you because, in our opinion, the success of research in this complex and rapidly developing field depends largely upon the prompt availability and evaluation of relevant publications, a task for which we should like to solicit the assistance of your readers.

In 1950, our Institute had initiated the publication of a series of reference volumes entitled "Annual Reports on Stress" (Acta Medical Publishers, Montreal) in which the entire current world literature is surveyed every year (usually between 2,000 and 4,000 publications). Up to now, we had to compile the pertinent literature partly from medical periodicals, monographs, and abstract journals; and partly from reprints sent to us by the authors themselves. Of all these, reprints proved to be the best source of data which we believed deserved prompt attention in our annual reports. Hence, in the past, we have sent out several thousand individual reprint requests to authors whom we knew were currently engaged in research on stress and allied topics. Even this procedure did not give us the wide coverage which would be desirable, because it is materially impossible

to contact all of these authors individually and it often takes too much time to get the requested reprints.

It is evident that, in order to ensure prompt inclusion of publications in the annual reports, these surveys must develop into a cooperative effort between the authors of original papers and the reviewers. This cooperation was greatly enhanced of late by the publication of announcements in several medical journals, encouraging investigators interested in stress research to send us their reprints for this purpose as soon as they become available.

We should be grateful if, by the publication of this note, you would also bring this problem to the attention of your readers.

We are Sir,

INSTITUTE OF EXPERIMENTAL MEDICINE AND SURGERY
UNIVERSITÉ DE MONTREAL
MONTREAL, CANADA

Very sincerely yours,
ALEXANDER HORAVA
HANS SELYE

January 22, 1953

American Trudeau Society

Medical Section of the National Tuberculosis Association

The Need for Rest Therapy in Connection with Long Courses of Drug Treatment for Pulmonary Tuberculosis

A Statement by the Committee on Therapy

Recent developments in the drug treatment and surgery of pulmonary tuberculosis offer a greater degree of control of the disease than forms of therapy available only a few years ago. As a consequence there is much interest in the possibility that prolonged rest in bed and other therapy of the disease, costly in time and money both to the individual and to society, might be less necessary than formerly.

Through its Committee on Therapy, the American Trudeau Society has been following a number of studies designed to cast light upon these questions, and will make every effort to keep the medical profession informed of progress made.

It should be emphasized that these questions have only recently been raised and that it has not been established that a reduction in the amount of rest therapy from that of past practice can be made without unfavorable effect. Where reduced amounts of bed rest are being tried it is for the purpose of study and is not to be regarded as standard practice.

In the very early stages of some investigations evidence suggests that, in highly selected cases, a moderate reduction in rest therapy during prolonged chemotherapy is not detrimental to the health of the individual. This does not apply to the average case of tuberculosis, however, and much more nearly complete follow-up studies will be needed to determine fully the effect of this change in therapy. Furthermore, there has been no clear indication that in advanced cases of tuberculosis the amount of rest therapy may be reduced with impunity even with fairly effective drug treatment.

Many allied problems associated with a possible reduction in the amount of bed rest indicated are in need of study. These include the manner in which non-bed-rest time is utilized and the details of the management of the associated chemotherapy which is so essential. The Society wishes to emphasize that, from the evidence now available, there is no indication that shortly there may be a significantly decreased need for beds for tuberculosis patients.

Charles A. Castle
David T. Carr
John Maxwell Chamberlain
Nicholas D'Esopo
John B. O'Connor
Karl H. Pfuetze
William B. Tucker
Carl W. Tempel

Robert H. Ebert, *Chairman*
Committee on Therapy

Report of Panel Discussion on Chemotherapy in Tuberculosis

The following record of a stimulating panel discussion at the 1952 annual meeting of the American Trudeau Society, held on May 27, 1952, at Boston, Massachusetts, was recently discovered by Dr. Floyd Feldmann who made it available to the Review. Although the opinions expressed are now one year old, the participants have good-naturedly agreed to the publication at this time of what they thought last year.

Except for a minute fragment of the record which was unaccountably lost, the version presented has received only minor editing, solely to improve readability.

The Review is particularly pleased to have this material for publication because it is believed that there are all too few forums today for the presentation of "opinion" sharpened by cross-questioning.

Because of Dr. McDermott's unavoidable return to New York, Dr. William B. Tucker acted as chairman of the meeting.

CHAIRMAN: This is going to be an extremely informal discussion. The men on the panel are not to be regarded as experts. They are the whipping boys. The experts are down in front. However, I am going to use the whipping boys more than the experts at the start this afternoon and fire some questions at them and see what kind of answers we get. There is no planned agenda. After a little of this "batting back and forth," questions from the floor will be invited. I am going to start right out and ask Dr. Hinshaw "Should chemotherapy be employed routinely in the therapy of idiopathic pleural effusion if presumably on a tuberculous basis, that is, in a tuberculin-positive person?"

DR. HINSHAW: I never liked the word routine. It's a bad word. If medicine were routine, we would not have to have physicians. I think this situation, however, calls for a great deal of judgment and a great deal of recognition of the potential seriousness of so-called benign idiopathic pleurisy with effusion.

CHAIRMAN: By the way, Corwin, I am going to hold you to two minutes.

DR. HINSHAW: It is not benign and it is not idiopathic. It is a dangerous form of tuberculosis. And certainly we use drug therapy much more frequently now than we ever did before. I would not say routinely because I believe there are circumstances where routine drug therapy would hardly be justified in the circumstances. Remember that routine drug therapy runs about a year or more of treatment. If you think the odds are sufficiently hazardous to the individual to justify a year or more of treatment, then by all means use it. And we frequently do use it.

CHAIRMAN: Would you say that such exceptions were very few in number?

DR. HINSHAW: I believe the exceptions are rather few because benign pleurisy with effusion is more frequent in those age groups most likely to have a long life ahead and most likely to have relapses of the disease, that is, young women in particular.

CHAIRMAN: Thank you very much.

I'm going to ask Dr. D'Esopo this question about minimal active pulmonary tuberculosis along exactly the same lines. Should drug therapy be employed routinely in such cases?

DR. D'ESOPO: I don't know whether it should or not but we are doing it. I'm fully aware of the fact that it is experimental therapy and, I think, justified by the high relapse rate in minimal tuberculosis. Besides relapse rate in minimal tuberculosis, I think the justification is the fact that minimal tuberculosis puts a lot of young people out of business for a long period of time. They eventually get well and very few of them die of minimal tuberculosis but I certainly think it is a type of tuberculosis worth investigating,

and it would be well if we dropped the word "minimal" and just said a small amount of tuberculosis.

CHAIRMAN: Now, another question, rather closely allied. This is addressed to Dr. Muschenheim. Should chemotherapy be employed routinely in the treatment of primary tuberculosis?

DR. MUSCHENHEIM: I share Dr. Hinshaw's objection to using any therapy routinely. I think in progressive primary tuberculosis it certainly should be used in all instances.

CHAIRMAN: Thank you very much, Carl. I think we are getting them broken in. Now I want to ask members of the panel here if they disagree with any of the statements which have been made about the use, rather the widespread use, of chemotherapy (we'll avoid the word "routinely") in pleural effusions, active minimals, and progressive primaries. Does anyone of the panel object? Yes, Dr. Tempel?

DR. TEMPEL: Dr. Hinshaw says that, if we start on that treatment, it should be continued for about one year. I'm not sure if he means that every pleural effusion case which is started on drug therapy would be treated for one solid year. I believe we are at that stage of investigation when we really can't answer that question; four to six months for the average case I would think would be adequate. I would hate to try to give everyone who has a pleural effusion a year of treatment.

CHAIRMAN: Now we don't want to get off on a side track yet on duration. Yes, Nick, what do you want to say?

DR. D'ESOPO: Oh, I would just like to ask Dr. Tempel why he said four to six months?

DR. TEMPEL: Drug treatment costs a lot of money, the injections are hard to give routinely for long periods, and for anyone to give PAS three times daily for one to two or more years really is accomplishing a great deal. I think we see eye to eye on the necrotic lesion and those which are not promptly reversible; but I believe those lesions that respond promptly, such as pleural effusion or minimal lesions, might well be treated at this stage of our investigations for a shorter period of four to six months. Some day I think we'll evaluate our cases on the stage at which we stop our treatment. Perhaps that will be at the arrested stage or at the inactive stage, as we are doing in meningitis.

CHAIRMAN: Stay away from this question of duration. I am going to come right back at Dr. Tempel and ask him this question. What is the role of reversible collapse procedures, such as pneumothorax and pneumoperitoneum, in patients receiving prolonged chemotherapy?

DR. TEMPEL: We are using prolonged chemotherapy on those lesions which do not respond promptly; in other words, in that particular group of cases where we are seeing more caseous-pneumonic tuberculosis. Therefore, the collapse procedures we are using are rarely pneumothorax but are more commonly pneumoperitoneum, and we carry such patients through the six- to twelve-month period and then apply surgical therapy. In our institution at least, temporary collapse procedures are primarily an adjunct to surgical treatment. And, of those two that I have mentioned, pneumoperitoneum has its greatest application because we find difficulty in applying pneumothorax to the caseous pneumonic lesion which does not respond promptly to treatment.

CHAIRMAN: In other words, Carl, if I understand you correctly, in prolonged chemotherapy you use a little pneumothorax and quite a lot of pneumoperitoneum in preparation for some localized resection in an appreciable number of cases. Is that correct?

DR. TEMPEL: That is about right.

CHAIRMAN: Dr. D'Esopo, would you care to speak on the same point, the role of reversible collapse procedures during prolonged chemotherapy?

DR. D'ESOPO: In our experience with prolonged chemotherapy, especially in the

regimen of a gram a day of streptomycin, we find a very high percentage of cavity closures; we hold off reversible collapse procedures until about the sixth to eighth month. If at that time the cavity is still present and it seems to be the kind that might respond to pneumoperitoneum, we use it. We also might use thoracoplasty at that time for the same reason. We believe it is dangerous to have open cavities late in the course of chemotherapy. The patient is almost certain to become positive and possibly resistant.

CHAIRMAN: Do you think pneumoperitoneum helps under those circumstances?

DR. D'ESOPO: I think the chief point I would like to make is the advisability of holding off with collapse procedures until you are sure the chemotherapy won't close cavities. It does in a very high percentage of cases.

CHAIRMAN: Dr. Hinshaw?

DR. HINSHAW: May I ask Dr. Tucker a question? Isn't it true that the data collected from the experience of the Veterans Administration would indicate quite clearly that those patients whose cavities were closed by drug therapy alone are more likely to stay closed if they also receive some form of collapse therapy?

CHAIRMAN: It is not my impression that there is any real satisfactory evidence from our data, Corwin.

DR. HINSHAW: I remember that was a topic for our discussion a year or two ago in one of the conferences and I got the impression . . . .

CHAIRMAN: The trouble, of course, was the technical statistical one, that the use of collapse therapy was not introduced in a random allocation manner, so that we were not at all confident that the two groups which were being compared were similar.

DR. HINSHAW: Early in the program we were very much disappointed at the large number of patients with cavitary disease who relapsed with reopening of the cavities a year or two after discontinuation of drug therapy. And for that reason collapse therapy was . . . .

CHAIRMAN: I don't think one can say from those data that the question was answered whether collapse therapy, if added to prolonged chemotherapy, has improved, or lessened, or has been indifferent to the results. That was prolonged therapy.

DR. TEMPEL: What you are referring to is chemotherapy of short duration?

DR. HINSHAW: Definitely yes at that time.

DR. D'ESOPO: I think it is true that, if chemotherapy is to be used for short duration, collapse therapy should be used almost simultaneously. I think the situation is very different with chemotherapy of long duration.

DR. HINSHAW: While you're on this subject, why deny a patient something which might help him or might shorten his period of illness? You have an excellent chance of helping him without adding to the risk.

CHAIRMAN: About how frequently is pneumoperitoneum used in the hospitals where you see patients, Dr. Hinshaw?

DR. HINSHAW: I would hesitate to put a percentage figure on it, but it is by far the most popular form of therapy, and we use it because I've seen no appreciable incidence of important hazard. It is a procedure essentially devoid of hazard, one which is readily controllable and reversible, and one which seems to add one more increment of benefit.

CHAIRMAN: Dr. Muschenheim, about how frequently is it used in the New York Hospital?

DR. MUSCHENHEIM: I can't give a percentage figure. I should certainly say it is used more frequently than pneumothorax. It probably is used about as frequently as surgical procedures, and I should estimate that probably the figure would be around 25 per cent.

CHAIRMAN: Colonel Tempel?

DR. TEMPEL: Of 414 patients discharged last year, who were treated to the inactive

stage, 130 received collapse procedures, predominately pneumoperitoneum, so it would be roughly, in our institution at least—,

CHAIRMAN: About 35 per cent. Next, how many?

DR. D'ESOPO: Oh, very few, maybe 5 or 10 per cent.

CHAIRMAN: Well, here we have the range. If anything, on this question of reversible collapse, I am sure that the general impression is that, if there is any area of agreement, it is that with prolonged and effective chemotherapy there is not quite the same urgent indication for reversible collapse therapy that there was previously. Would there be general agreement with that? Well, you are good enough at least not to interrupt immediately. I'd like to come back to Dr. Hinshaw and ask him, "What are the indications and contraindications for chemotherapy of pulmonary tuberculosis today?

DR. HINSHAW: Perhaps it would be easier to list the contraindications than it would the indications. The factors which have been enumerated here of course are the expense, discomfort, et cetera. I believe the best way of answering that question would be to tell you what I would tell a patient who came to me and asked me why he had not received drug therapy. I usually answer him in this manner if he has minimal disease: That we are ready to apply this weapon if and when it seems necessary immediately, but it is a project of no small dimensions. It is a thing which we must consider carefully because we do believe that the average patient who receives drug therapy should have it continued for a year or even longer. At any time when the trend seems to be even slightly adverse, we will institute drug therapy. It turns out that the average patient does receive drug therapy, but by no means all of them do. An active progressive lesion is an indication for antimicrobial therapy. Contraindications are those in which we hesitate to subject the patient to that much financial and personal trauma, in which we might fear toxic manifestations, when we have aged patients or patients with impaired renal function, at which time toxic reactions to streptomycin are more usual. I also think that those who are unable to tolerate PAS should not receive drug therapy at all unless the situation is definitely urgent. When PAS must be withdrawn, we withdraw streptomycin also unless the disease is quite a serious one.

CHAIRMAN: You do not substitute other drugs.

DR. HINSHAW: Now, with isoniazid on the scene, that of course can be changed.

CHAIRMAN: In general then, Dr. Hinshaw, you feel that for most cases of tuberculosis which require hospital care there is an indication for chemotherapy. But in the minority there are a few individuals for whom for various reasons there are contraindications. Is that right?

DR. HINSHAW: Yes that is well stated.

CHAIRMAN: Dr. D'Esopo, what is your answer to such a question?

DR. D'ESOPO: I agree almost completely except that I would not wait until the patient fails to improve. I use chemotherapy immediately. The reason for withholding chemotherapy in my opinion does not depend on the lesion; it depends on the patient and on those things which Dr. Hinshaw mentions. I think we are beyond the stage where we put a patient to bed and see how he gets along without chemotherapy.

CHAIRMAN: That's a very important point, I think. I'll address the next question to Colonel Tempel. In view of the demonstrated advantage of prolonged chemotherapy, especially in cases being treated for the first time, what are the indications when such chemotherapy may be safely terminated?

DR. TEMPEL: That is almost the treatment of tuberculosis. I think the long therapy should be embarked on when the lesion does not respond promptly to therapy; in other words, those lesions . . . .

CHAIRMAN: This is discontinuation of therapy.

DR. TEMPEL: It depends on each individual case. If there is complete reversibility of all those elements which are not necrotic and we end up with a lesion which is showing little or no change for two or three months, we are getting to the end of the usefulness of the drug. In other words, if this is active tuberculosis, we should be thinking of surgery. At our instituton it is usually somewhere in the neighborhood of six to twelve months before that stage arrives. In other words, the average patient admitted has a component of mixed lesions in which we treat the reversible component. Long-term treatment would not be in order for those so-called localized areas which show no change. The surgeon could well be called in the first one or two months for resection if it is active disease. Our object is to get a recovery and get that patient out as soon as possible; but those with extensive disease who still respond must be continued until there is no change in that lesion, ordinarily in order that we may get the greatest localization of the disease; and the smallest degree of resection, I think, is an individualized problem and is worked out along that line. In practice it works out at six to twelve months, more often eight months or more.

CHAIRMAN: Thank you very much, Carl. I'm going to ask Dr. Muschenheim this question in a slightly different way. Are there any objective criteria of the stability of the lesion by X-ray observation, which are helpful in determining the duration of chemotherapy?

DR. MUSCHENHEIM: Well, those criteria which Colonel Tempel mentioned, the stability by X-ray, principally. I think the major decision really is arbitrary and one just has to decide on the basis of experience what one is going to consider the average term of therapy. Of course, there will be individual variations and cases must be individualized. I would just like to say, in relation to the use of chemotherapy in tuberculosis in general, that our experience at the New York Hospital is perhaps a little different from the experience you have been hearing about, since we have a very small service, which, in recent years since the antimicrobials have been developed, has become largely a research service. All of our patients, I think without exception except the occasional contraindication mentioned, receive chemotherapy. The point I would like particularly to make is the value of very prolonged chemotherapy in patients who even two or three years ago we might have considered as virtually hopeless cases. We recently have had patients who became streptomycin- and PAS-resistant whom we then started on various other antimicrobials which we were investigating. One such patient has been in the hospital for two and one-half years, has had five or six different drugs and has also had some surgery. That patient had two upper lobes which were really completely destroyed and now has no open cavities and has had a negative sputum for four or five months.

CHAIRMAN: In other words, you are emphasizing certain advantages of very, very prolonged chemotherapy and of using other procedures.

Dr. Hinshaw?

DR. HINSHAW: I have often quoted Nick D'Esopo on this and I hope I've quoted him correctly. I have often quoted him as saying "that drug therapy should be continued so long as the patient continued to improve, perhaps by any criteria whatsoever, and then for a few months longer."

CHAIRMAN: Nick?

DR. D'ESOPO: Yes, I haven't changed my mind about that, I don't believe.

CHAIRMAN: No, Dr. D'Esopo doesn't change his mind easily.

DR. D'ESOPO: I think that as long as a cavity is still present you should never stop chemotherapy. It is fairly conclusive that the sputum always becomes "positive" again, no matter how long therapy has been going on, and the organisms are apt to be resistant. The point I would particularly like to make is that the objective criteria we have are

principally the examinations of sputum and X-rays. I don't think that should be adhered to. The situation is somewhat as it used to be in the arsenical therapy of syphilis. We picked an arbitrary period of time, eighteen months as I remember, and we were not guided by Wassermann reaction, reflexes, eyegrounds, et cetera. Our goal now is different. Our goal is to affect the bacilli, the viability of the bacilli, and not the reversal phase of the disease or cavity closure or anything like that. So we must treat blindly, and treatment should be continued for months after all objective criteria have been satisfied. I have no idea how long that should be, but I think a minimum of a year is all right for 1952.

CHAIRMAN: That is a very practical application and advice on this problem from someone who has thought about it a great deal. I'm glad Dr. D'Esopo mentioned this question of viability or the question of nonviability of tubercle bacilli in necrotic nodules or inspissated cavities. I am going to ask Dr. Hinshaw this question. Now that with prolonged streptomycin and PAS therapy the viability of bacilli in lesions is in question, what are the indications for resecting such inspissated cavities or necrotic residuals locally?

DR. HINSHAW: Of course, our surgeons don't resect them all as some surgeons have been doing. I think those surgeons who have been resecting them all would admit that it is something of a study. But when the lesion appears to be the type which might reopen, and I speak particularly of these spherical inspissated cavities which you mention, resection would seem to be less hazardous than letting the patient continue to carry such a lesion; or if the disease is delimited to one lobe or one segment, even though it appears to be arrested, particularly if it be a younger person who has a long life to lead. The longer he lives, the greater opportunity for subsequent reactivation. It has to be based on our judgment of what the probabilities are that this disease will become reactivated at some subsequent time. We have particular fear of these rounded spherical lesions which are inspissated cavities.

CHAIRMAN: Nick, I'm going to let you talk on that same subject but ask you another question at the same time. How safe is it judged to be to permit a necrotic residual, a centimeter in diameter, as the only demonstrable pulmonary focus after prolonged chemotherapy to remain in the lung instead of subjecting such a lesion to localized resection?

DR. D'ESOPO: Well, in so far as patients who have been treated for a year or more are concerned, those patients have done quite well. There has been a maximum follow-up of two and one-half years.

CHAIRMAN: You mean without resection.

DR. D'ESOPO: Without resection. The question is, how many patients like that do we have to have and for how long do we have to follow them? It is certainly premature to advocate chemotherapy as definitive therapy, but we do have lots of cases that we can't resect for one reason or another and they are controls in a way; in our hospital we are resecting those whom we can resect and are willing to be resected when the lesions are so distributed that the surgeon thinks he can resect them, and having the others serve as "controls." But we really don't know which lesion to resect once the cavities have become inspissated.

CHAIRMAN: Does anyone else on the panel care to speak on that question?

DR. MUSCHENHEIM: I should like to say just a word about it. I think that the practitioner of medicine who is active in the tuberculosis field runs pretty much of a follow-up clinic. And, certainly, a great deal of his work is merely follow-up. I have seen a great many patients with these lesions who go many, many years with no trouble at all.

CHAIRMAN: Dr. Hinshaw?

DR. HINSHAW: Perhaps one other element should be brought in, namely, how certain are we, how confident are we, that this patient will submit to careful follow-up? We have very frequently submitted patients to resection when we thought they were persons who would not be liable to cooperate with follow-up care, such as, the chronic alcoholic, the patient of low economic status, the patient who lives in outlying communities; or because of some social or economic or psychological barrier to thorough follow-up. Under such circumstances, we are more likely to submit that patient to radical surgery.

CHAIRMAN: It seems to me that this necrotic nodule we are talking about for the moment is very intimately related to the problem of minimal tuberculosis on which Dr. Lincoln and Dr. Mitchell reported on Monday. If a necrotic residual had the potentialities for relapse in as high a percentage of instances as was reported by these and other observers, the question must be answered whether there is that same potential after prolonged chemotherapy as there was in the cases studied before.

Dr. D'Esopo, do you have any thoughts along that line? You might like to comment on the pathologic studies of Dr. Medlar.

DR. D'ESOPO: These minimal lesions that we have resected and Dr. Medlar has examined have all the morphological requisites for relapse. They are filled-in cavities; bronchi are open and filled with inspissated material. They do contain tubercle bacilli, so, morphologically, they look as if they might easily relapse. The difference now is the question of the viability of the tubercle bacilli in these lesions. Of course we don't have a definitive answer to that. If the bacilli are really dead, then the lesion is bacteriologically, not morphologically, cured; and that patient should not relapse. Another point that would be interesting to compare is under what circumstances do minimal lesions remain stable. In the past many people have remained well with minimal tuberculosis because they have so modified their lives. I think another one of our goals in modern therapy is to treat minimal tuberculosis in such a way that the person can immediately forget that he has ever had tuberculosis; not go back to work in five or ten years, but go back to heavy work. Not only relapse but conditions under which relapse occurs are important.

CHAIRMAN: Dr. D'Esopo has touched on a very important point. In effect, we are trying to raise our standards of the outcome of the treatment of pulmonary tuberculosis. We are no longer satisfied with the best possible results which we used to obtain.

I want to go on to another question which still bears upon the same question. Dr. Tempel, what is the optimum time for the resection of necrotic residuals in relation to prolonged chemotherapy either in terms of months or of such an end point as the absence of sputum or demonstrable change by X-ray?

DR. TEMPEL: May I ask, that was an active changing lesion when we started?

CHAIRMAN: Yes.

DR. TEMPEL: Well, I think that was partially answered already. One would wait till this lesion practically showed no change in order that it might be removed at the time when the least amount of tissue would be required for removal, so that the time for the average case certainly would be around eight months.

CHAIRMAN: Dr. Muschenheim, how would you answer that same question?

DR. MUSCHENHEIM: Well, I think the trend is very definitely to wait until lesions are very well stabilized, unchanging, and have reached a maximum amount of regression; that is the course we have followed. I might say that we have been very conservative about resecting lesions in which there is no demonstrable cavity.

CHAIRMAN: I want to ask Dr. D'Esopo what is the relative therapeutic efficacy of two regimens: (*1*) 1 gram of streptomycin and PAS, both daily, and (*2*) 1 gram of streptomycin every third day or twice a week, and PAS daily?

DR. D'ESOPO: The data collected during the last streptomycin conference of the Veterans Administration, Army, and Navy study units suggested that these two regimens were equally good. I think the criticism of those data is the fact that their criteria were X-ray change and sputum bacteriology. I think we have a new criteria now and that is the bacilli's viability in resected lesions. While our data are premature, we have some evidence to suggest that the regimen of streptomycin twice a week results in more viable bacilli in resected lesions. The clinical importance of that, I think, is unknown.

CHAIRMAN: Is that at the same time, the same duration of therapy? Is it possible that at a later period the interrupted streptomycin treatment might give the same result? Have you analyzed it that way?

DR. D'ESOPO: These patients who have received streptomycin twice a week have been resected under the same criteria. In some cases because the patient did not have any place to go, and so forth, we actually delayed operation for a year or so. We then resected and found viable bacilli. Now the other piece of evidence (just clinical, not evidence really) is the impression that patients with large cavities and those who are very ill seem to do better with one gram a day. Whether after a while they cannot be treated with one gram twice a week I don't know. The important point now, I think, is to keep the question open. We really do not yet know the best regimen; probably there is no best regimen; perhaps the regimen must be made to fit the patient.

CHAIRMAN: We are discussing several variables still. We do not yet know what may finally be the best regimen combining streptomycin and PAS, so we are rapidly touching on some of the variables. Now here's a variable I shall ask Dr. Hinshaw about. Is there any evidence that the same total duration of streptomycin and PAS therapy administered continuously is better than the same total duration administered intermittently, that is, with rest periods in between?

DR. HINSHAW: I have been very much impressed by the data collected by Dr. D'Esopo and his group showing distinct superiority of treatment in those situations in which treatment was continuous rather than interrupted. I have been able to verify it in a sufficient number of cases to believe that it may be a rule that there is a real hazard in discontinuing treatment so long as organisms continue to multiply or we have reason to believe that they are capable of a resurgence to power. May I also comment in this matter of one gram a day *versus* one gram twice a week? All of us, I am sure (many of us at least), have had occasion to observe patients who did not respond symptomatically to one gram twice a week, that is, by reduction of fever and improvement of cough and so on, but who did respond as soon as treatment was intensified to one gram a day. I have even taken patients off and seen a recurrence of fever and put them on more intensive treatment and seen the temperature go down again. I think many of us feel that during the acute phases of the disease, during the early phases of the disease, while patients are suffering symptoms (particularly such symptoms as fever), one gram a day may well be justifiable for a period of at least several weeks; and I think there is growing evidence that it is unwise to discontinue treatment with the thought of starting it again if and when necessary.

CHAIRMAN: With regard to the point which you make about the use of daily or intermittent streptomycin in the acute phases, I would like to report for one of my associates in the Veterans Administration who is in a hospital in the southeastern part of the United States. He had a great deal of difficulty selling his associates on the treatment of the acute forms of tuberculosis, particularly in Negroes, with the twice-a-week streptomycin regimen. However, he persisted because he was anxious to determine the relative value of the regimens, and I believe I have understood him correctly to report to me today

that he is now convinced that one is just as good as another even in those acute forms. Well, there is a lot more that could be said on these many variables. Now, I am going to ask Dr. Muschenheim a sort of summary question, What in his opinion is the best regimen available today combining streptomycin and PAS in the treatment of tuberculosis, just those two drugs?

DR. MUSCHENHEIM: I think the best way to answer that is to tell what we are doing. We have followed what I think probably has been the path of least resistance, of treating patients by and large with one gram twice a week combined with daily PAS, 12 grams a day in divided doses. I am not nearly so convinced as the gentleman you mentioned that one gram twice a week is as effective as one gram daily. Neither am I so convinced that one gram daily is as effective as 2 grams daily. I appreciate that this is based on clinical impressions and that such opinion is not supported by statistical evidence. I am not at all sure that such fine differentials are very susceptible to statistical analysis. But I think in the last analysis it does come down to what we are and are not willing to do; and there again we come to the patients who need chemotherapy most urgently and most efficiently. Certainly, in miliary tuberculosis I would not treat a patient with one gram twice a week and I think there are very few others who would.

CHAIRMAN: Corwin?

DR. HINSHAW: Would it be fair to state that the number of patients who require a gram a day, or even more, are so few as not to affect large volume statistics?

DR. MUSCHENHEIM: I'd agree with that.

CHAIRMAN: Dr. Tempel, what is your opinion? Would you care to express a different opinion?

DR. TEMPEL: We have been giving intermittent doses of streptomycin since 1947. We are convinced it is as effective as the daily use. We are using, however, 2 grams instead of one in those persons who weigh more than 120 pounds. In our reported series of 103 patients who were followed carefully, there was no worsening in that group during the 120-day observation period. Like others, we do not treat miliary tuberculosis or meningitis with intermittent streptomycin. We treat that serious form with daily drug treatment. I might say that very few patients who come to us have very fulminating or very toxic symptoms or are running much fever. In our recent study to find cases to study the effect of isoniazid on symptoms, we found only a few in our first hundred that even had fever. By the time they are transferred to us from all over the country, or from overseas stations, they are free of fulminating symptoms so that perhaps I don't have the same problem which would be seen in the city hospital where these patients come in acutely and seriously ill with high fever. I really feel that in our series it makes no difference. We use the intermittent treatment all the time.

CHAIRMAN: Thank you. Now Nick, what do you say about it?

DR. D'ESOPO: Haven't I answered that?

CHAIRMAN: I think you have. I just wanted to give you a chance.

DR. HINSHAW: Army tuberculosis and even Veterans Administration tuberculosis is not the same as county hospital tuberculosis, particularly if you live in a big city and have a lot of chronic alcoholics and recurring patients. That is an entirely different problem. Army tuberculosis particularly is easier to treat.

CHAIRMAN: We will take that up some other time. We won't go into that now. I think you experts have listened very patiently for forty-five minutes to us whipping boys up here "passing it back and forth." We have gone over quite a number of the aspects of treatment of pulmonary tuberculosis with streptomycin and PAS. I would like now to throw the discussion open to the floor for ten to fifteen minutes, if there is that much interest, restricting it still to the problem which has been covered here, namely, strepto-

mycin and PAS therapy, and we shall return to the subject of certain other drugs used in the treatment of tuberculosis. Is there an expert who would like to ask a question? Dr. Waring?

DR. JAMES WARING: I do not think the experts gave a complete answer to the question whether you would treat primary tuberculosis with chemotherapy.

CHAIRMAN: No, all they said was they would treat progressive primary.

DR. WARING: That's right; and your question was would you treat primary tuberculosis? My answer to that would vary considerably whether it was an infant or young child or whether it was an older person.

CHAIRMAN: I'll let you have three minutes, Dr. Waring.

DR. WARING: If you had, for instance, a resident, an intern, a student, or a nurse who came in with a conversion of a tuberculin test from "negative" to "positive" and without the X-ray sign of a real lesion in the chest, I'd like to ask the experts if they would treat such a case with chemotherapy? My answer to that is that I would treat that person with chemotherapy. If he had no X-ray lesion in the lungs and no constitutional symptoms, I still would give him the benefit of chemotherapy. I think we have been too afraid of chemotherapy. We ought to use it to prevent subsequent surgery and not delay it until subsequent surgery becomes necessary. When it comes to the infant, I haven't had enough experience to know. I know Dr. Lincoln is opposed to giving chemotherapy to all infants with primary tuberculosis, and I would have to bow to her judgment; and yet, if I were left on my own, I would be inclined to give chemotherapy even to the infant or young child who comes down with primary tuberculosis. That is my answer to my own question.

CHAIRMAN: Thank you very much Dr. Waring. You have touched on the important problem of the ever-broadening indications for the chemotherapy of tuberculosis and the contraindications to delay. Is Dr. Lincoln here? I wonder if she would care to speak on the question of the chemotherapy of primary tuberculosis in childhood? Would you please?

DR. EDITH LINCOLN: We still feel that we would not treat the asymptomatic primary with chemotherapy regardless of the size of the lesion or the age of the child. In other words, we would still not so treat an infant, even with a very large lesion, if that infant did not have fever. The reason for this is twofold. In the first place, it has not been shown that a primary lesion disappears any more rapidly with streptomycin than it did previous to chemotherapy. In the second place, no one has been able to show that it prevents complications such as miliary and meningitis. And in the third place, there is always the question of the emergence of resistance. The other reason we in our service do not treat it by chemotherapy is that by treating only the complications—the serious complications—of primary tuberculosis and not treating asymptomatic primary tuberculosis, we have succeeded in reducing our mortality in a very heavily infected group of children from about 24 per cent to less than 3 per cent since the days of chemotherapy.

CHAIRMAN: Thank you very much Dr. Lincoln. Is there any discussion from the floor? Dr. Riggins?

DR. H. MCLEOD RIGGINS: My question is directed, not only to the experts on the podium, but to the expert who just asked the $64 question. Would one treat the nurse who comes in with a "negative" tuberculin test and the tuberculin test becomes "positive"? Would Dr. Waring treat that patient, not only with chemotherapy, but would he take her out of nursing and put her on bed rest or partial bed rest, or pneumoperitoneum, or would he send her away to the mountains, preferably of course to Denver?

CHAIRMAN: Dr. Waring did not use all of his three minutes. Dr. Waring?

DR. WARING: Of course, that's a difficult question and I anticipated it. You are under

a heavy responsibility. A nurse comes to you and says "My tuberculin test has converted from "negative" to "positive;" and the X-ray of my chest is perfectly clear. And what am I going to do?" Now if you say, "No, don't take chemotherapy because two, three, four, ten, or fifteen years from now you may need surgery," and this girl develops active pulmonary tuberculosis during the next year or more (and there's ample evidence to indicate that a certain percentage will do that), why then she will say to you and to herself, "Why didn't you recommend chemotherapy at that time?" I don't think it's logical to use chemotherapy after you've got a whole lot of tuberculosis and not use it when you have only a little tuberculosis. And that is my feeling about it. I think that we ought to "give it the works" while it's small in size and in quantity and not wait until it gets very bad and then say, "*Now* is the time to use chemotherapy."

CHAIRMAN: Is there anyone up here at this table who would like to speak on the question of the indications for the chemotherapy of the primary? Dr. Hinshaw?

DR. HINSHAW: I just want to mention one point. As our weapons are multiplied, we become less and less alarmed by streptomycin resistance.

DR. JOHN M. RIDGE: Might I ask the experts if they would differentiate between the primary infection in a child and that in a young adult? In my experience with children, the primaries do not progress, even under the most unfavorable home surroundings. But would the experts care to make a difference in the case of the young adult?

CHAIRMAN: Dr. Muschenheim?

DR. MUSCHENHEIM: In the first place, I think it is rather difficult to make a diagnosis of primary tuberculosis in the adult. Certainly, my experience with these young nurses and hospital personnel and medical students whose tuberculin has "converted" recently, while reviewing a great many of their films routinely, has been that it was rather unusual in the first place to see any lesion at all. If one did see a lesion, it was usually one that had the characteristics of the ordinary early infiltrate, so-called, of the reinfection phase. Whether some of those were actually primary or not I don't know. I do think that, when one does see a lesion in an adolescent or in a young adult, it is most likely to be progressive without treatment; in those cases I would certainly treat them. I would like, if I may, to record my own reactions to Dr. Waring's question with respect to treatment of the person whose only evidence of primary infection is conversion of the tuberculin test. My feeling about that would be that I certainly would be in favor of treating such a person if we had a more satisfactory type of chemotherapy than we have now. I think to subject a person to the discomfort and the difficulties of taking PAS for a year and streptomycin twice a week hardly justifies the treatment where the risk of serious trouble, at least in the immediate future, is as small as it appears to be.

DR. HINSHAW: Is there such a thing as primary tuberculosis?

CHAIRMAN: No; you can't ask that one. Dr. Carr.

DR. DAVID CARR: The generally recommended dose of PAS is 12 grams per day in three or four divided doses. Many patients aren't able to take this amount. What does the panel believe is the minimal acceptable dose in order to make it safe to continue streptomycin therapy?

CHAIRMAN: Before he gets away from that microphone, I'll turn it back to him. What does he personally think is acceptable?

DR. CARR: I am looking for help.

CHAIRMAN: No, no, now don't get off the hook.

DR. CARR: I guess one shouldn't ask questions. I don't think we know. I think there is a definite need for investigation of this because of the fact that we don't know; but I wanted to find out what the experts had to say.

CHAIRMAN: All right, we'll find out. We'll begin with Dr. Tempel?

DR. TEMPEL: I would say 12 grams because I believe there were studies some years back that showed that, when the dosage dropped down as low as 8 grams, resistance to streptomycin, at least in the combined use of the two drugs, developed.

CHAIRMAN: It was a very informal study and also rather inconclusive. Let's ask Nick D'Esopo.

DR. TEMPEL: Let me give you another one though. Streptomycin every third day and PAS daily resulted in no resistance. However, when I used both drugs every third day I got a 30 per cent resistance to streptomycin. I would say that that gives good evidence that you have to use . . . .

CHAIRMAN: Dr. Carr's question, however, was that, if given daily, what is the minimum dose. Dr. D'Esopo?

DR. D'ESOPO: Twelve grams is the best dose used now, but I agree we don't know. Dr. Muschenheim?

DR. MUSCHENHEIM: I'm in the same situation as Dr. Carr and Dr. D'Esopo. I don't know. Dr. Hinshaw?

DR. HINSHAW: I don't know either, but I have a strong suspicion it may be as low as 6 or 8 grams per day, and there is some evidence that 6 grams per day is adequate. This was in the *New England Journal of Medicine*.

CHAIRMAN: I think we would all agree that question deserves further serious and intensive investigation.[1] There must be other questions about the indications for streptomycin and PAS therapy which someone else in the room would like to ask.

DR. PERKINS: I would like to ask Dr. D'Esopo how long he would continue combined therapy in an individual who has had a resection for a localized lesion? Presumably this individual has had preoperative combined therapy, we'll say, for three, four, or five months.

DR. D'ESOPO: I might give you our present plan. We continue chemotherapy routinely for four months after resection if everything is favorable. If there are some vague indefinite shadows left after resection—shadows we can't interpret and don't know whether they are blood or new lesions and so forth—we continue chemotherapy until we are satisfied that the residual shadows are not tuberculous lesions. There isn't much rationale really in continuing therapy for four months after resection. However, we have adhered to it to make our studies more homogeneous. What we have in mind is to take care of whatever spillage occurs.

CHAIRMAN: Well, that is a question which is bothering a great many of us. I am sure we don't know the final answer. Are there other questions from the floor?

DR. GOWRY: I would like to ask the panel of experts how long to give streptomycin and PAS to a patient who has active minimal tuberculosis and complications which followed after the start of the streptomycin. A week after she started the streptomycin and PAS, she developed an eye condition which an ophthalmologist called tuberculous, a definite tuberculous lesion of the eye, and he advised continuance of streptomycin-PAS. About a month after that, she had a convulsion which the neurologist called a left temporal lesion, etiology unknown. They advised exploration, which was not done. The patient refused to have it done. Now she's been perfectly fine. The eye condition has been clear for several months now, the lungs are completely clear, and she is completely asymptomatic. How long should streptomycin and PAS be carried on? She has had several months of treatment now.

[1] For such a study, the reader is referred to Medical Research Council Investigation, Brit. M. J., May 31, 1952, No. 4769, 1157.

CHAIRMAN: Dr. Hinshaw, would you care to answer that question?

DR. HINSHAW: Just on the possibility that this may have been a tuberculoma and knowing the extreme hazard of such a condition, I would continue that patient on treatment for no less than one year, and, more likely, two years.

CHAIRMAN: Thank you. Other questions from the floor?

DR. M. R. LICHTENSTEIN: I would like to ask Dr. D'Esopo whether he uses pneumoperitoneum so little because he thinks the chemotherapy is so good that he doesn't need pneumoperitoneum or because he thinks pneumoperitoneum is so poor that he doesn't want to use it?

CHAIRMAN: O.K. Nick?

DR. D'ESOPO: The rate of cavity closure is so high with daily streptomycin-PAS that in many cases pneumoperitoneum is not necessary to close cavities. I assume that is the only purpose of pneumoperitoneum. Cavities close without it. Another thing of practical importance is this. Cases with cavities have been started simultaneously on chemotherapy and pneumoperitoneum, and, after six or eight months or so, everything is fine and the cavity closes but you don't know what did it. You don't know how long to continue pneumoperitoneum. When you do something and something good happens, there is a tendency to ascribe the good result to what you did. I think pneumoperitoneum confuses the issue.

CHAIRMAN: Thank you. Dr. Lichtenstein, anything more?

DR. LICHTENSTEIN: I would like to know if there is any choice in method in using PAS, in liquid form or in cachets.

CHAIRMAN: Anyone want to answer that? Guess not, sorry. On this question of pneumoperitoneum, it is my own feeling that no one has ever done a control study, an adequate control study. I feel that it is of value in certain types of cases, but the degree of value has been decreased by the presently available effective prolonged therapy. Now if there is any merit in that, I'd like to ask Dr. Trimble if he would care to say something about pneumoperitoneum.

DR. HAROLD TRIMBLE: Well you asked for it. Here it is. I'm very happy that Dr. D'Esopo and his group are working under randomized conditions, and so forth, getting as much scientific information as can be gotten, taking into consideration individual patients. I personally don't work that way. As far as I am concerned, this patient has to have the thing that he needs according to my best knowledge of today. However, I can't throw away a background of years ago and I can be perfectly sure that we accomplish things with collapse therapy, particularly pneumoperitoneum over pneumothorax, that we could not do in the days when we had pneumothorax alone. I just can't throw that out. I think that medical experience is worth something. And I can't give you randomized figures, but we have made very careful studies. There are a large group of men who have; and those men do not choose to work in a randomized atmosphere although I'm not criticizing that and I'm happy that some men do. You wouldn't want to be the randomized patient if you came to me, I'm sure. You would want to be given the best thing I could give you at the moment and not be the blank control. I feel reasonably sure about that.

CHAIRMAN: Thank you Dr. Trimble.

DR. TRIMBLE: I'm not quite through. I have a question to ask Dr. D'Esopo also. When Dr. Hinshaw asked him a question, he stated there was no randomization available in connection with chemotherapy and collapse therapy. Is that correct?

DR. HINSHAW: I think that's correct.

DR. TRIMBLE: And then, a little bit later when he was talking about excision therapy

—the little snip and so forth and so on—he stated they have a group of patients in which they cannot do surgery. And he said that those were his controls; he put quotations around "controls," I know.

CHAIRMAN: That is "of a sort."

DR. TRIMBLE: Yes "of a sort." That's correct. Now I should like to know if there is a difference in those two groups of patients and why he chooses to exert such strict criteria in one group and such rather loose criteria in the other although I admit there were quotations around the "rather loose criteria"?

CHAIRMAN: I'm not going to give Dr. D'Esopo an opportunity to answer that question, Harold, because I don't think a question of the type of investigation is pertinent to our discussion this afternoon. I think that is somewhat outside the sphere. Dr. Lichtenstein, did you have another question that we interrupted back there? No, Dr. Pfuetze, excuse me.

DR. PFUETZE: I would like to direct a question to Dr. Tempel. I think Carl, that you are the only one in the country using two grams twice a week in your interrupted regimen. Am I correct in that?

DR. TEMPEL: I don't know.

DR. PFUETZE: My question then is this. Do you continue on this regimen because you and your group are convinced that that is the best, or is it still a study in an attempt to find the best regimen, or the dosage?

DR. TEMPEL: We are on our seventh combined regimen and we have used it mainly for the sake of comparison. After having used combined therapy since 1948 with this dosage schedule, we believe that it is preferable to use the two gram dosage. I really can't say. Our statistics in the VA, Army, and Navy studies would lead us to believe that there is essentially no difference between it, if used as we use it, and the one gram dosage.

DR. PFUETZE: Thank you that's what I want.

CHAIRMAN: Dr. D'Esopo tells me that he would like to answer Dr. Trimble and we will give him a short time for that.

DR. D'ESOPO: I think my silence might be misunderstood. I don't want to give Dr. Trimble the impression that we are randomizing cases. If the patient does not do well with chemotherapy alone, then we apply collapse therapy. Exactly the situation of many years ago when we used bed rest. Then, if the patient didn't do well on bed rest, we used collapse therapy. Now I think in general we are using chemotherapy like bed rest.

CHAIRMAN: Your name please, sir.

DR. CASE (Washington, D. C.): Dr. D'Esopo has several times used the expression "chemotherapy alone" and I was wondering if he means alone without bed rest or alone with bed rest, or what he had in mind?

CHAIRMAN: I think that is my error. I meant at the very start of this little panel discussion this afternoon to say that when we are talking about chemotherapy we of course assumed that the other usual methods of treatment were employed.

DR. CASE: But I think pneumoperitoneum has been used enough to be considered a fairly usual type of treatment; and, since he speaks of chemotherapy alone without pneumoperitoneum, I was wondering if he was just treating his patients with chemotherapy without regard to bed rest as well.

CHAIRMAN: I think that we will not have time to go into that further. I want to make just one further comment on the pneumoperitoneum question. Harking way back to that N.T.A. meeting in Milwaukee in 1937, when many of you will remember that there were a number of papers on pneumoperitoneum (some from our friends on the west coast and some from other parts of the country), there was some disagreement in the

results; and in the closing discussion it was recalled how one of the forceful speakers from the west coast said that they had one distinct advantage. They had wonderful air on the west coast and many had driven there in their cars and they would be delighted to let the air out of their tires for those in the rest of the country to employ. I'm going to have to cut this discussion on streptomycin and PAS off.

(Part of record missing)

DR. HINSHAW: How did you give five grams a day to these patients and how much would it cost? I don't have a slide rule with me.

DR. TEMPEL: The drug (terramycin) was furnished us by a kindly manufacturer for our research studies and I have no idea of the cost. I want to say, however, that I am cost-conscious and our PAS as we give it is only 10 cents a day. I know that's a lot cheaper than terramycin.

CHAIRMAN: Dr. Tempel, at the present time would you consider substituting terramycin for the PAS in combination with streptomycin in the occasional individual (discussed by Dr. Hinshaw) who can't take PAS?

DR. TEMPEL: Yes I would. In fact, we do that. We have found that in our PAS series 5 per cent of persons develop rashes and fevers and are unable to take the drug. Now, at the present time (when I left the hospital), there were 591 individuals on the drugs, so that might mean as many as 25 patients in this series. To the individual patient it is an extremely important thing that we have a drug as a substitute. Maybe isoniazid will be that drug later.

CHAIRMAN: Thank you very much. Now I'm going to come back to that, Carl Muschenheim, with a question about another drug. What is the place of amithiozone in the chemotherapy of tuberculosis?

DR. MUSCHENHEIM: I have had very little experience with it at any time. From what I have read and learned from colleagues, I think there is very little place for it at all; and in patients who can no longer take streptomycin I think we have other drugs that we can now use.

CHAIRMAN: Is there any disagreement at the table? Corwin, how about using amithiozone in mucosal tuberculosis, enteritis, or something of that sort?

DR. HINSHAW: Well, with so many other drugs which are easier to use and available, we have nearly discontinued the use of amithiozone. For some time we did use it routinely in those patients who were unable to tolerate PAS and learned to our discouragement that it did not delay the development of streptomycin resistance.

CHAIRMAN: Thank you. I have rather deliberately left not too much time for questions on the new drug, isoniazid, because that was so very adequately and extensively covered in the special session last evening. However, to complete the picture in this informal discussion, there are some questions I'd like to ask my associates. Dr. D'Esopo, on the basis of the limited evidence available, which is the preference for the average patient with tuberculosis in whom there is an indication for chemotherapy, isoniazid or streptomycin and PAS?

DR. D'ESOPO: Oh, I think of streptomycin and PAS as chemotherapy and the other as isoniazid.

CHAIRMAN: That's a little strong.

DR. D'ESOPO: I think that latter drug is still in the investigative stage.

CHAIRMAN: In other words, you are really saying that in a patient who needs treatment and who has not had treatment so that he already represents a drug therapy failure the drugs of choice continue to be for the time streptomycin and PAS. Is there question

or discussion on that by others on the panel? That does not mean, of course, that there might not be a change in the future. Carl, were you going to say something?

DR. MUSCHENHEIM: Well, I would like to say that I don't believe that that question can really be answered and I think to say that it is in the investigative stage is perhaps begging the question a little bit. I think that we have evidence certainly that isoniazid is an effective agent. We don't know yet whether it is as good as streptomycin and PAS. Certainly, we don't know whether it will prove to be so in the long run, but I do think it is one that may be considered and I think that possibly in some of these patients in whom the indications are not very compelling or immediate, it is sometimes quite reasonable to use the isoniazid, reserving the streptomycin and PAS the way we used to reserve streptomycin alone before we had PAS.

CHAIRMAN: Nick, I hear you muttering.

DR. D'ESOPO: Well, I think the most important point now about isoniazid is the fact of resistance. Resistance does occur. We all know patients who were treated with streptomycin alone in 1946 whose futures were certainly jeopardized. They were made streptomycin resistant. There is no doubt that this drug is going to be good when we know how to use it. I certainly don't think we should make patients isoniazid resistant, especially those who don't really need chemotherapy as an emergency measure.

CHAIRMAN: This very subject is back of the next question which I was going to ask. Dr. Muschenheim, should isoniazid if used in such a patient be given alone or in combination, and, if in combination, in combination with what?

DR. MUSCHENHIEM: May I first make one comment on Dr. D'Esopo's last comment and that is that, if isoniazid is not much of a drug, what difference does it make if resistance does develop?

DR. D'ESOPO: I didn't say it wasn't much of a drug. I said I think it has a good future, but not alone. What we really want in chemotherapy is protracted bacteriostasis, and it is impossible to get protracted bacteriostasis with a drug to which resistance occurs. We never got it with streptomycin alone. I think now that potentially we may do people a lot of harm by making them isoniazid resistant. I think isoniazid is an excellent drug, but not alone.

CHAIRMAN: Does that clarify your position, Carl, a little, or do you care to go on?

DR. MUSCHENHEIM: I don't want to protract the discussion on that at all and I agree with Dr. D'Esopo in the essentials. With regard to the question whether it should be used alone or in combination and, if so, in combination with what, there again I think it is very difficult to say. My own feeling is that, although there are strong indications that relatively early emergence to predominance of resistance will be a very common limiting factor, we really do not yet know that. Hence, my inclination would be to continue with it alone until we have more information.

CHAIRMAN: Corwin?

DR. HINSHAW: We've had a rather extensive experience with isoniazid which was well under way before the publicity came about. We have now between 120 and 130 patients on treatment. About a third get isoniazid alone, a third get it with PAS, and a third get it with streptomycin. We haven't tabulated our results in general, but take one item, namely weight gain. Weight gain in those who got isoniazid alone for a period of one to four months was 2.9 pounds. With PAS it was 4.3 pounds, and with streptomycin it was 6.4 pounds, more than twice as much. And other criteria seem to be similar in the three groups.

CHAIRMAN: What were your clinical impressions?

DR. HINSHAW: Our general impressions are that those who received streptomycin

with the isoniazid have done very much better than any other group, but those who got PAS with isoniazid have done better than those who got isoniazid alone.

CHAIRMAN: Dr. Hinshaw, for a patient whom it has been decided to treat with isoniazid, would you use it alone or would you use it in combination?

DR. HINSHAW: I would use it in combination.

CHAIRMAN: Either with PAS or streptomycin or, preferably, streptomycin?

DR. HINSHAW: I'd use it with streptomycin because it is a better drug than PAS. And in a patient who has tuberculous meningitis, perhaps miliary tuberculosis, I believe it might even be necessary. I think we would be compelled to use isoniazid because of its penetration into the cerebrospinal fluid.

CHAIRMAN: I was going to ask Dr. Muschenheim about using isoniazid in tuberculous meningitis. Carl, would you care to say something?

DR. MUSCHENHEIM: I see we have only about a minute left, and that is a very large question.

CHAIRMAN: Take two or three minutes. We have time.

DR. MUSCHENHEIM: With respect to the use of isoniazid, the encouraging thing about it is the observation which Dr. Hinshaw just made that it is well distributed into the cerebrospinal fluid. Last evening I mentioned that we had some twelve patients with miliary tuberculosis, four of whom also had meningitis under treatment; that four of those had died, three of meningitis. We have in most instances combined streptomycin with isoniazid so it is very difficult to interpret results. We have at least one meningitis patient who has not received any intrathecal streptomycin and who is doing well, but has received intramuscular streptomycin along with the isoniazid. We have another patient with meningitis who would fill all the criteria, except that we have not yet proved the diagnosis, who has received isoniazid alone and is doing well. We feel that isoniazid will certainly be a very valuable adjunct, almost certainly, let us say, in the treatment of meningitis; and possibly it may obviate the necessity for intrathecal treatment. That is certainly not yet determined.

CHAIRMAN: Do you feel, as Dr. McDermott does, that there are only two drugs currently available today that can be used effectively in the treatment of miliary tuberculosis, namely, streptomycin and isoniazid?

DR. MUSCHENHEIM: I think one might add the possibility of viomycin.

CHAIRMAN: I want to ask Dr. Tempel a question. In streptomycin-resistant cases, what is the antituberculous drug of choice today in your opinion?

DR. TEMPEL: That's a tough one. I think if the patient is on treatment which is a combination of streptomycin and PAS and there is a need for continued therapy, the indications would be for the continuance of the streptomycin and PAS. I think that one might substitute isoniazid now in such a case, but that's highly theoretical at this stage of investigation. I believe that, that being our best weapon, there is no proved substitute for it. We have used viomycin, however, in a series of, I think, some 80 patients intermittently; were there a real need for drug therapy, I feel certain that it could be substituted. In fact, it would be a good substitute. It has been definitely proved that that drug is effective. There are so many side reactions, however, that it is difficult to use.

CHAIRMAN: That's with daily viomycin.

DR. TEMPEL: That's with intermittent, every third day.

CHAIRMAN: Thank you Carl. I want to ask Dr. Hinshaw about his ideas on the intravenous administration of PAS.

DR. HINSHAW: I am sure that prior to the advent of isoniazid there was an important place for intravenous PAS, and one of these situations is tuberculous meningitis. Un-

questionably the most spectacular results that have ever been reported in tuberculous meningitis to my knowledge are those of Loeffler and Moeschlin in Zurich where they were able to secure very very prolonged and apparently permanent arrest with very little residual in the overwhelming majority of their patients, 75 to 80 per cent, or more.

CHAIRMAN: How much did they use?

DR. HINSHAW: They used around 40 grams a day of sodium PAS intravenously; the equivalent of about 30 grams of PAS.

CHAIRMAN: Used every day continuously?

DR. HINSHAW: Continuously every day for weeks and months. It is very difficult but it can be done and has been done; and we have also used it in patients with streptomycin-resistant organisms who required drastic surgery for surgical prophylaxis, and we have reason to believe that it may have helped.

CHAIRMAN: Well, there we have rapidly touched on some of the other drugs used in the antituberculous drug program. Now there might be a few pertinent questions from the floor. Dr. Sweany?

DR. H. C. SWEANY: I've heard the mention of viomycin on one or two occasions. I wonder if the panel would like to comment on the possibilities of its use; for instance, in the substitution in streptomycin-resistant cases, I have seen some fairly good results.

CHAIRMAN: Dr. Tempel, could you answer Dr. Sweany on that very briefly?

DR. TEMPEL: I think the drug could well be used. At present, however, it is at the level of investigation and not available commercially, so it is not available for general use for substitution. The studies to date would lead us to believe that in urgent cases it might well be substituted. As I stated, we have a series on intermittent treatment that makes its use not prohibitive, although reports upon its use daily indicate that the reactions were rather numerous and, perhaps, one would say that it would be contra-indicated certainly for a period as long as four months.

CHAIRMAN: Dr. Muschenheim?

DR. MUSCHENHEIM: I can only agree with what Dr. Tempel has said. For circumstances entirely unrelated to our opinion of the drug, we have not had occasion to use it recently but, when we were using it, we felt that it was certainly the only drug which approached streptomycin in activity and that possibly it very closely approached streptomycin. I certainly think that there are indications for its use occasionally in streptomycin-resistant cases.

CHAIRMAN: Are there other pressing questions? If not, I declare the panel session adjourned.

Report[1] on Team Projects for the Recovering Tuberculosis Patient in Tuberculosis Hospitals in the United States

This report is an attempt to measure the degree to which a concept of rehabilitation as an integral part of tuberculosis control is currently applied in American tuberculosis hospitals and sanatoriums. The fact that no less than 180 American treatment institutions, with a combined bed capacity of over 40,000, are currently reported to utilize rehabilitation teams[2] has not previously been reported.

The criterion for inclusion has been the meeting at regular intervals of clinical personnel with an extraclinical group—usually including nurses, occupational therapists, social workers, vocational counselor, teachers, and others—for the purpose of determining suitable exercise or study privileges, current problems of patients and their families (particularly as they affect cooperation in treatment), and/or the consideration of post-hospital outlook for the patient. Numerous other institutions also utilize some extraclinical personnel but are not currently reported to have established a periodic teamwork procedure. Collation of this report has been made possible by courtesy of constituent state tuberculosis associations.

Medical administrators are cordially invited to notify the Committee on Rehabilitation for the American Trudeau Society, of which Dr. William G. Childress, of Grasslands Hospital in Valhalla, New York, is chairman, of undeserved omissions from this listing.

The marked significance of this list is evidence of a growing attention to more permanent medical results by clinical personnel which ensures planning and guidance for patients with favorable prognosis whether or not they are eligible for official vocational rehabilitation services. Nevertheless, the efforts of such official services have been enormously facilitated by such medical leadership, as indicated by new growth in the number of placements in employment by state agencies of clients with a history of tuberculosis. The national total for the fiscal year 1952 was 5,833 placements, an increase of 18 per cent over the 1950 total. An analysis of records placed by state vocational rehabilitation agencies in 1951 indicated that in that year 64 per cent of the total were referred from tuberculosis hospitals and sanatoriums.

Hospitals and sanatoriums reported to be utilizing teamwork procedures are:

Alabama	
Jefferson Tuberculosis Sanatorium (SP)	Birmingham
District No. 1 Sanatorium (MC)	Decatur
Montgomery TB Sanatorium (SP)	Montgomery
California	
Barlow Sanatorium (SP)	Los Angeles
Bret Harte Sanatorium (MC)	Murphys
Butte County Hospital (Co)	Oroville
Charles Cook Hastings Home (SP)	Altadena
City of Hope (P)	Duarte
General Hospital (Co)	Riverside
General Hospital (Co)	Long Beach
County Hospital (TB Department)	Santa Clara

[1] This is a report submitted *to* the American Trudeau Society by the writer and does not represent an official report on the subject by the Committee on Rehabilitation.

[2] Diagnostic Standards, National Tuberculosis Association, 1950, p. 64.

Weimar Joint Sanatorium (MC)	Weimar
Tulare-Kings County Hospital (Co)	Springville
COLORADO	
Craig Colony Sanatorium (SP)	Denver
Denver General Tuberculosis Ward (M)	Denver
Denver General Out-patient Clinic (M)	Denver
Jewish Consumptives' Relief Society (SP) Sanatorium	Spivak
Lutheran Sanatorium (SP)	Wheatridge
Mennonite Sanatorium (SP)	La Junta
Mesa Vista Sanatorium (P)	Boulder
National Jewish Hospital (SP)	Denver
Sunnyrest Sanatorium (SP) (Half Way House Conference)	Colorado Springs
Swedish National Sanatorium (SP)	Englewood
CONNECTICUT	
Cedarcrest (S)	Hartford
Undercliff Sanatorium (S)	Meriden
Laurel Heights (S)	Shelton
Uncas-on-Thames (S)	Norwich
The Seaside (S)	Waterford
Gaylord Farm (P)	Wallingford
DELAWARE	
Brandywine Sanatorium (S)	Marshalltown
Edgewater Sanatorium (S)	Marshalltown
DISTRICT OF COLUMBIA	
Glendale Sanatorium (M)	Glendale, Md.
Gallinger Municipal Hospital (M)	D. C.
Upshur Street Rehab. Hospital (M)	D. C.

Key to Abbreviations:
S—State Co—County M—Municipal SP—Semi-private
MC—Multi County P—Private

FLORIDA	
S. E. Florida Tuberculosis Hospital (S)	Lantana
Central Florida Tuberculosis Hospital (S)	Orlando
S. W. Florida Tuberculosis Hospital (S)	Tampa
W. T. Edwards Tuberculosis Hospital (S)	Tallahassee
GEORGIA	
Muscogee County Tuberculosis Hospital (Co)	Columbus
ILLINOIS	
Lake County Sanatorium (Co)	Waukegan
Springfield Sanatorium (Co)	Aurora
Edward Sanatorium (P)	Naperville
Winfield Hospital (SP)	Winfield
La Salle County Sanatorium (Co)	Ottowa
Rock Island County Sanatorium (Co)	Rock Island
Peoria Municipal Sanatorium (M)	Peoria
Elmgrove Sanatorium (Co)	Bushnell
Oak Knoll Sanatorium (Co)	Mackinaw
Fairview Sanatorium (Co)	Normal
Hillcrest Sanatorium (Co)	Quincy

St. Johns Sanatorium (P)	Springfield
Mt. Vernon State Hospital (S)	Mt. Vernon
Chicago and Cook County	
Municipal TB Sanitarium (M)	Chicago
Oak Forest TB Hospital (M)	Oak Forest
Indiana	
Sunnyside Sanatorium (Co)	Indianapolis
Healthwin Hospital (Co)	South Bend
Indiana State Sanatorium (Co)	Rockville
Irene Byron Sanatorium (Co)	Ft. Wayne
James O. Parramore Hospital (Co)	Crown Point
Silver Crest TB Hospital (S)	New Albany
Flower Mission Hospital (M)	Indianapolis
Iowa	
Broadlawns Hospital (Co)	Des Moines
Sunnyslope Hospital (Co)	Ottumwa
Pine Knoll Sanatorium (Co)	Davenport
State Sanatorium (S)	Oakdale
Kansas	
State Sanatorium for Tuberculosis (S)	Norton
Eleanor Taylor Hospital	Kansas City
Kentucky	
Waverly Hills (MC)	Waverly Hills
Maryland	
Mt. Wilson State TB Hospital (Co)	Baltimore
Henryton State TB Hospital (Co)	Carroll County
Baltimore City Hospital (M)	Baltimore
Mt. Pleasant Sanatorium (SP)	Reisterstown
Victor Cullen State TB Hospital (S)	Frederick County
Massachusetts	
Essex County Sanatorium (Co)	Middleton
Middlesex Sanatorium (Co)	Waltham
Plymouth County Hospital (Co)	Hanson
Rutland State Sanatorium (S)	Rutland
Westfield State Sanatorium (S)	Westfield
Michigan	
American Legion Hospital (SP)	Battle Creek
Arthur Kimball Sanatorium (Co)	Battle Creek
Copper Country Sanatorium (Co)	Hancock
Grand View Hospital (Co)	Ironwood
Ingham County Sanatorium (Co)	Lansing
Jackson County Sanatorium (Co)	Jackson
Morgan Heights Sanatorium (Co)	Marquette
Muskegon Sanatorium (Co)	Muskegon
North Michigan Sanatorium (S)	Gaylord
Oakland County Sanatorium (Co)	Pontiac
Pinecrest Sanatorium (MC)	Powers
Pine Crest State Sanatorium (S)	Oshtemo
Saginaw County Hospital (Co)	Saginaw
Michigan State Hospital (S)	Howell

MINNESOTA	
Glen Lake Sanatorium (Co)	Oak Terrace
Nopeming Sanatorium (Co)	Nopeming
MISSISSIPPI	
Mississippi State Sanatorium (S)	Sanatorium
MISSOURI	
Koch Hospital (M)	St. Louis
Missouri State Sanatorium (S)	Mt. Vernon
MONTANA	
State TB Sanatorium (S)	Galen
NEBRASKA	
Nebraska State Hospital (S)	Kearney
NEW HAMPSHIRE	
Pembroke Sanatorium (SP)	Concord
N. H. State Sanatorium (S)	Glencliff
NEW JERSEY	
Clyde M. Fish Memorial Hospital	Northfield
Bergen Pines (Co)	Ridgewood
Marcus W. Newcomb Hospital (Co)	New Lisbon
Essex County Sanatorium (Co)	Verona
B. S. Pollak Hospital (Co)	Jersey City
F. W. Donnelly Hospital (M)	Trenton
Roosevelt Hospital (Co)	Metuchen
Allenwood Sanatorium (Co)	Allenwood
Shonghum Mountain Sanatorium (Co)	Morristown
New Jersey Sanatorium for TB (S)	Glen Gardner
Bonnie Burn Sanatorium (Co)	Scotch Plains
NEW MEXICO	
State Sanatorium (SP)	Socorro
NEW YORK	
New York City	
Bellevue (M)	Manhattan
City Hospital (M)	Welfare Island
Kings County (M)	Brooklyn
Metropolitan (M)	Welfare Island
Willard Parker (M)	Manhattan
Municipal Sanatorium (M)	Otisville
Neponsit Beach (M)	Queens
Triboro (M)	Queens
Seaview (M)	Staten Island
Seton Hospital (M)	Bronx
Montefiore Hospital	Bronx
Country Branch	Bedford Hills
St. Joseph's Hospital	Bronx
Upstate	
Herman M. Biggs Hospital (S)	Ithaca
Mt. Morris TB Hospital (S)	Mt. Morris
J. N. Adam Hospital (S)	Perrysburg
Onondaga Sanatorium (Co)	Syracuse
Niagara Sanatorium (Co)	Lockport

Iola Sanatorium (M)	Rochester
Trudeau Sanatorium (SP)	Saranac Lake
Grasslands Hospital (Co)	Valhalla
Pawling Sanatorium (Co)	Wynantskill
North Carolina	
West N. C. Sanatorium (S)	Black Mountain
Durham County Sanatorium (Co)	Durham
Mecklenburg Sanatorium (Co)	Huntersville
Forsythe County Sanatorium (Co)	Winston-Salem
Ohio	
Sunny Acres (Co)	Cleveland
Oregon	
State Hospital (S)	Salem
Pennsylvania	
Pittsburgh TB Sanatorium (M)	Pittsburgh
TB League Hospital (SP)	Pittsburgh
Cresson State Sanatorium (S)	Cresson
Mont Alto Tuberculosis Hospital (S)	Mont Alto
Philadelphia General Hospital (M)	Philadelphia
All Saints Hospital (SP)	Chestnut Hill
Rossmere Sanatorium (SP)	Lancaster
Eagleville Sanatorium (SP)	Eagleville
Philadelphia Hosp. for Contagious Diseases (M)	Philadelphia
Rhode Island	
Rhode Island State Sanatorium (S)	Wallum Lake
Charles V. Chapin Hospital (M)	Providence
South Carolina	
State Sanatorium (S)	State Park
Pinehaven Sanatorium (Co)	Charleston
Utah	
State TB Sanatorium (S)	Ogden
Virginia	
Pine Camp Hospital (M)	Richmond
Granby Sanatorium (M)	Norfolk
Blue Ridge Sanatorium (S)	Charlottesville
Piedmont Sanatorium (S)	Burkville
Catawba Sanatorium (S)	Salem
Washington	
Firland Sanatorium (Co)	Seattle
Riverton Hospital (SP)	Seattle
Laurel Beach Sanatorium (P)	Seattle
Mountain View Sanatorium (Co)	Lake View
Edgecliff Sanatorium (Co)	Spokane
Wisconsin	
Wisconsin State Sanatorium (S)	Statesan
Lake View Sanatorium (Co)	Madison
Sunny Rest Sanatorium (Co)	Racine
Pinehurst Sanatorium (Co)	Janesville
Lake Tomahawk State Camp (S)	Lake Tomahawk

Pureair Sanatorium (Co)	Bayfield
Middle River Sanatorium (Co)	Hawthorne
River Pines Sanatorium (SP)	Stevens Point
Mount View Sanatorium (Co)	Wausan
Mount Washington Sanatorium (Co)	Eau Claire
Riverview Sanatorium (Co)	Kaukauna
Rocky Knoll Sanatorium (Co)	Plymouth
Maple Crest Sanatorium (Co)	Whitelaw
Morningside Sanatorium (SP)	Madison
WYOMING	
Wyoming Tuberculosis Sanatorium (S)	Basin

HOLLAND HUDSON

NOTES

FIRST INTERNATIONAL CONVENTION OF X-RAY TECHNICIANS

The First International Convention of X-Ray Technicians will be held at the Royal York Hotel, Toronto, Canada, June 29 through July 2, 1953, and will be sponsored by the Canadian Society of Radiological Technicians and the American Society of X-Ray Technicians.

Refresher courses are offered for two hours each morning. Eight courses will be presented, four by Canadian and four by American technicians. These courses are offered to beginners as well as to advanced technicians. Additional information and advanced enrollment may be obtained by contacting Beatrice Hurley, R. T., Registrar, St. Catherine Hospital, East Chicago, Indiana.

The afternoon sessions will be devoted to joint sessions of the CSRT and ASXT, at which time technical papers and essays will be presented by technicians of both societies and by distinguished radiologists on invitation.

Two memorial lectures will be given:

1. Canadian—*Welch Memorial Lecture* by E. A. Petrie, Director, Department of Radiology, St. Joseph's Hospital, St. John, New Brunswick, Canada.

2. American—*Jerman Memorial Lecture* by Russell H. Morgan, Professor of Radiology, Johns Hopkins University, Baltimore, Maryland.

One need not be a member of either of these sponsoring organizations to enjoy the activities of the First International. Guest badges are available which will allow anyone to join convention activities and array of social functions.

NECROLOGY

Dr. David Weisbrod Crombie, London, Ontario, Canada
Dr. John Dwight Davis, Long Beach, California
Dr. Abraham E. Jaffin, Jersey City, New Jersey
Dr. Arthur J. Logie, Miami, Florida
Dr. Oscar Lotz, Milwaukee, Wisconsin
Dr. Lawrence W. Nehil, Indianapolis, Indiana
Dr. Maxim Pollak, Memphis, Tennessee
Dr. Kumud Sankar Ray, Bengal, India
Dr. Moses J. Stone, Boston, Massachusetts
Dr. Nelson W. Strohm, Buffalo, New York

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 67 MAY, 1953 ABST. NO. 5

CLINICAL STUDIES, TUBERCULOSIS

Primary Tuberculosis.—Most children who have a pulmonary primary tuberculous complex, composed of a small parenchymal lesion with involvement of regional lymph nodes, have no constitutional reaction. Within one or two weeks after infection, an unknown proportion develop fever, malaise, lymphadenitis, or sensitivity reactions such as erythema nodosum or phlyctenular conjunctivitis. The real, immediate danger of the primary infection is the widespread dissemination of tubercle bacilli in a small proportion of cases. Localized complications, such as bronchial erosion or occlusion or pleural effusion, are most likely to arise in the first two years after infection and in children infected within the first two years of life. Neither chemotherapy nor hospital care is recommended for the well child with a primary pulmonary infection. If the primary infection is accompanied by constitutional symptoms, the patient is put to bed at home; if the symptoms persist longer than a month, chemotherapy and sanatorium care should be considered even when there is no roentgenographic evidence of dissemination. The primary focus may extend locally; granulation tissue and caseous material may cause bronchial occlusion. Complete occlusion may be transient and due to pressure from enlarged glands, but is generally due to direct extension of the tuberculous process. Incomplete obstruction leads to distal emphysema: complete obstruction is followed by collapse. Healing is accompanied by bronchial stenosis or distortion, lung scarring, and bronchiectasis. Bronchoscopy has been disappointing in effecting re-aeration. Primary tuberculosis of the ileocecal lymph nodes may simulate acute appendicitis. Tuberculous lymphadenitis in the neck, groin, or axilla is sometimes accompanied by a demonstrable primary mucosal or cutaneous focus. The regional nodes should be excised to prevent suppuration or sinus formation; this procedure should be covered by a short course of streptomycin.—*The management of children with primary tuberculosis, F. J. W. Miller, Brit. M. J., November 8, 1952, No. 4792: 1015.*—(*E. A. Riley*)

Bronchiectasis and Primary Tuberculous Infection.—Among 35 patients with evidence of bronchial obstruction secondary to a tuberculous infection, 29 were bronchoscoped. Of these, 11 had evidence of partial or complete bronchial occlusion, 5 had an acute nonspecific infection, 11 had a chronic pyogenic infection, and 3 had no evidence of endobronchial disease. Among 28 patients who had bronchographic studies, 20 had bronchiectasis. Autopsy protocols of 186 children who died of tuberculosis showed 15 to have bronchiectasis as a complication of primary tuberculous infection. Bronchoscopic examination is important when there is clinical evidence of bronchial obstruction or roentgenographic evidence of pulmonary involvement in a tuberculous process of greater extent than a simple primary focus; bronchoscopic relief of the obstruction may be possible. Abnormal physical signs, symptoms, and roentgenographic findings occurring after the primary tuberculous infection has had reasonable time to subside may indicate superimposed bronchiectasis. This can be satisfactorily investigated only by bronchography, and may require surgical therapy to control the symptoms of secondary pyogenic infection.—*Bronchial obstruction and bronchiectasis complicating primary tuberculous infection, J. B. Hardy, D. F. Proctor, & J. A. Turner, J. Pediat., December, 1952, 41: 740.*—(*M. J. Small*)

ACTH and Miliary Tuberculosis.—A 35-year-old woman, while under therapy with corticotropin (ACTH) for acute disseminated lupus erythematosus, developed acute miliary tuberculosis followed by several cold abscesses. In this case, corticotropin may have acted both as a nonspecific and as a specific desensitizing agent; it may also have induced a profound depression of mesenchymal tissue as demonstrated by the occurrence of miliary tuberculosis.—*Miliary tuberculosis in a case of acute disseminated lupus erythematosus treated with ACTH, B. Walker, Brit. M. J., November 15, 1952, No. 4793: 1076.*—(*E. A. Riley*)

Cortisone and Tuberculosis.—A 37-year-old woman with an arrested tuberculous lesion in the right upper lobe received cortisone for rheumatoid arthritis. In the twelfth week of therapy symptoms of a respiratory infection developed. The chest film showed a pneumonic infiltration in the area of the old tuberculous lesion. The sputum was positive for acid-fast bacilli.—*Exacerbation of tuberculosis during treatment with cortisone, E. F. Traut & J. Ellman, J.A.M.A., July 26, 1952, 149: 1214.*—(*H. Abeles*)

Sugar Content of Effusions.—The free sugar content of various effusions from 40 cases was measured by the Schaffer or Folin-Wu method with fluorine added to avoid rapid glucolysis if the analysis could not be done immediately. The albumin content of the effusions was measured by refraction, the number and type of cells were observed, and the presence of tubercle bacilli was determined by culture. Simultaneous blood sugar determinations were made. High sugar concentrations of 1.25 and 0.87 gm. per 100 cc. occurred in pleural fluids containing less than 120 or as many as 2,100 leukocytes per cu. mm. whether lymphocytes or polymorphonuclear leukocytes predominated. The concentration of albumin in an effusion did not parallel the sugar content. Thus, 1 gm. of sugar per 100 cc. was found as often in anasarca effusions containing only 12 gm. of albumin per 100 cc. as in polyserositis effusions with 55 gm. of albumin per 100 cc. The inflammatory nature of an effusion, suggested by its high albumin content, was not necessarily paralleled by a high content of sugar, which varied from zero to 2 gm. per 100 cc. When tubercle bacilli were present, the free sugar content was always low, ranging from zero to 0.1 gm. per 100 cc. Nontuberculous effusions always contained at least 0.1 gm. of sugar per 100 cc. In 50 per cent of the nontuberculous cases, the free sugar concentration was definitely higher than the blood sugar concentration and there seemed to be no correlation between the two values.—*Note sur le dosage en sucre dans les epanchements, Fr. Thys, Acta tuberc. belg., October, 1952, 43: 397.*—(*A. T. Laird*)

Electrocardiograms in Pulmonary Tuberculosis.—In a group of 100 abnormal tracings of patients with pulmonary tuberculosis, 4 electrocardiograms were interpreted as being due to myocardial damage, and 96 were apparently due to mediastinal shift and rotation. Abnormalities were noted in various leads. It appeared that multiple unipolar chest and augmented unipolar extremity leads did not aid materially in the differentiation of damage from displacement. They served, instead, to help in the explanation of the abnormalities in the standard leads. In the course of this study, some findings of note were recorded: Deviation of the RS-T segment is not necessarily associated with myocardial damage, and a pattern consisting of an inverted P wave and R wave and inverted T wave in aV_L frequently occurs in mediastinal displacement. The RS-T deviations as well as the T changes in the precordial leads in the electrocardiogram of patients with pulmonary pathology demand particular caution in their interpretation (Author's summary).—*On some aspects of unipolar electrocardiography in the presence of pulmonary pathology, Th. T. Fox, H. Berger, & C. E. Meidt, Am. Heart J., November, 1952, 44: 747.*—(*G. C. Leiner*)

Tuberculous Sigmoidovesical Fistula.—A proved tuberculous sigmoidovesical fistula closed, and marked improvement of the blad-

der mucosa was noted eight weeks following fecal diversion by means of a transverse colostomy. Resection of the involved sigmoid revealed extensive caseous tuberculosis of the submucosa with tuberculous diverticulitis of the sigmoid. The age of the tuberculous lesion in the sigmoid is open to question in that the patient had no evidence of active pulmonary disease and a negative sputum for eight years under good supervision. This would suggest a hematogenous route as the most likely method of inoculation.—*Tuberculous sigmoid-vesical fistula, J. V. Comer, Ann. Surg., November, 1952, 136: 901.*—(*M. J. Small*)

Tuberculosis in a Dog.—Tuberculosis is rare among dogs in the United States. It occurs most often in animals one to five years old and produces weight loss, cough, and lymphadenopathy about the head or neck. A male dachshund approximately one year old had loss of appetite, apathy, and a temperature of 102.6°F. It soon began to vomit, cry, and carry the left hind leg off the ground; rales were found in both lungs. Despite aureomycin and penicillin, it failed rapidly. Tuberculosis was suspected fifteen days after the animal was first seen and an intradermal tuberculin test was positive. The dog was killed on the seventeenth day. The postmortem examination showed caseous lesions in the lungs and mediastinal lymph nodes with thickened intestinal walls.—*Tuberculosis in a young dachshund, A. B. Shopmaker & E. E. Epstein, Vet. Med., December, 1952, 47: 525.*—(*L. B. Hobson*)

Lobectomy for Pulmonary Tuberculosis.—The low mortality and relatively early results have been impressive in the use of lobectomy in the treatment of 219 consecutive tuberculous patients. Streptomycin, 2 gm. every third day, with 12 gm. of *p*-aminosalicylic acid daily were given to 98.2 per cent of the patients. In the presence of known active disease, six to twelve months of properly supervised therapy was generally adequate prior to lobectomy. Thoracoplasty of the upper portion of the thoracic cage was made part of the program for upper lobectomy on the premise that the expansion of the remaining lung tissue to fill the uncollapsed hemithorax favored overdistention and probably increased the activity of reactivated tuberculous lesions. An upper lobectomy and a five-rib thoracoplasty appreciably conserved pulmonary function when compared to the usual multiple-stage thoracoplasty removing seven or more ribs. Lobectomy with thoracoplasty seems preferable to selective artificial pneumothorax in irreversible and irreparable destruction of lung substance. Lobectomy was performed on 146 patients for persistent cavitary disease, on 57 for noncavitary disease, and on 16 for suspected but unproved tuberculosis. The indications for lobectomy were: (*1*) tuberculoma not suitable for segmental resection; (*2*) persistent cavitary disease involving principally one lobe, i.e., after six to twelve months of bed rest including antibiotic therapy or after six months with unexplained positive sputum after thoracoplasty, particularly if bronchostenosis of the lobe bronchus is present; (*3*) persistent chronic active noncavitary tuberculous lesions involving principally one lobe; and (*4*) certain suspected but unproved chronic tuberculous lesions confined principally to one lobe, exclusive of tuberculoma. Of 20 lobectomies done for thoracoplasty failure, cavitation was present in 19, and active endobronchial disease was present in 33 per cent of the lobes removed. Sputum conversion occurred in 14 of these cases. The experience with lobectomy for thoracoplasty failure is superior to that with revision thoracoplasty and cavernostomy. Among the 146 patients with cavitary disease were 20 thoracoplasty failures and 21 tuberculomas. In all, 112 patients have been followed one or more years since surgery; sputum conversion occurred in 80 per cent. The average blood loss at operation and during the first twenty-four hours, as determined by blood volume studies using the Evans blue dye, was 2,495 cc. Complications have been few; bronchopleural fistula developed in 3.2 per cent, empyema in 2.7 per cent, and spread of the disease in only 2 per cent. The

mortality has been 0.75 per cent. With increasing early detection of tuberculosis, modern chemotherapy, and safer surgical methods, lobectomy will steadily increase as the method of surgical management.—*Lobectomy for pulmonary tuberculosis, J. H. Forsee, Ann. Surg., November, 1952, 136: 828.—(M. J. Small)*

Pulmonary Resection.—The complications and deaths which occurred within sixty days of thoracic surgery are reported in 114 patients with tuberculosis who had a pneumonectomy, lobectomy, or segmented resection performed during the period March 1, 1950, to March 1, 1952. There were 47 pneumonectomy patients, 8 of whom died; 7 developed a bronchopleural fistula. Empyema without bronchopleural fistula developed in 5 cases. In the lobectomy group, there were 60 patients, with 4 deaths, 3 bronchopleural fistulas, and no empyema. None of the 7 segmental resection patients died, and a bronchopleural fistula developed in one instance. The entire group was further classified according to normal risk (87 cases) and desperate risk (27 cases). There were 8 deaths and 7 bronchopleural fistulas in the former group, and 4 deaths and 4 bronchopleural fistulas in the latter group. The over-all mortality within a sixty-day period was 10 per cent. The development of bronchopleural fistula during this period of time was also approximately 10 per cent.—*Quelque remarques à propos de l'exérèse pour tuberculose pulmonaire, A. P. Naeff, Schweiz. Ztschr. Tuberk., 1952, No. 9: 540.—(E. Dunner)*

Pneumoperitoneum Treatment.—The status of 200 patients ten years after pneumoperitoneum was reviewed. Almost all of the patients had far advanced disease and several forms of collapse therapy prior to pneumoperitoneum treatment. Complications resulting in discontinuation of treatment arose in 20 patients. Follow-up studies showed that 110 patients had died. In one-half of the 20 patients in whom autopsies were performed, free fluid was found in the abdomen. In 2 patients a plastic exudate covered the viscera, in other patients fibrotic plaques covered part of the exposed viscera. Of the 90 living patients, 38 were working.—*Late results of artificial pneumoperitoneum in pulmonary tuberculosis, ten year follow-up study of two hundred patients, E. Morris & E. Bogen, J. A. M. A., July 19, 1952, 149: 1120.—(H. Abeles)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Acute Laryngeotracheobronchitis.—Among 650 necropsies on children, there were 119 cases of bronchopneumonia, most of which were terminal and secondary infections. Many of the 41 cases of chronic lung infections were associated with inhalation of regurgitated gastric contents. There were 35 cases in which the primary cause of death appeared to be an acute intrinsic infection of the tracheobronchial tree in which obstruction of the air passages was the essential feature. There were one case of probable angioneurotic edema of the larynx and glottis, 2 cases of laryngeal infection with subglottic inflammation and muscosal ulceration, and 3 cases of extreme vascular engorgement of the mucosa with extensive necrosis of the epithelium and lymphocytic infiltration. In these 3 cases, coagulase-positive *Staphylococci* were cultured at autopsy. The largest group of 18 cases revealed an intact ciliated epithelium, but the lower trachea and bronchial tree contained an extremely tenacious gray exudate extending to the smaller, but rarely to the terminal, bronchioles which either distended or collapsed. Many of the bronchial gland ducts and acini were dilated with inspissated material. The final group of cases consisted of 11 children in whom inflammatory changes in the form of purulent fluid in the lumen, cellular infiltration of bronchi and bronchioles, and vascular engorgement were the predominating features. The pathology is best expressed clinically as a "capillary bronchitis" and this group differed clinically from the preceding only in that there was a longer interval between severe

dyspnea and death. Ages ranged from six weeks to twelve years. Most of the cases occurred between November and April. Except for the 3 cases in which *Staphylococci* were demonstrated, no pathogenic organisms were cultured. Acute laryngeotracheobronchitis apparently accounts for more deaths in the six-week to twenty-four-month age group than all the generally recognized and reported infectious diseases. The clinical condition of the last two groups seems related to the viscosity of the secretions, which may be due to a defect in the normal process of liquefaction. Since several cases followed the administration of sulfonamides, it seems possible that antibacterial agents may interfere with the growth of liquefying bacteria. Since the major pathology is one of obstruction, chemotherapy is likely to be ineffective; and since death seems to be due chiefly to mechanical suffocation by abnormal mucus secretion, treatment should be directed at maintaining an airway.—*Acute laryngeotracheobronchitis in children: A study of the incidence and pathology, J. L. Emery, Brit. M. J., November 15, 1952, No. 4793: 1067.—(E. A. Riley)*

Obliterative Laryngeotracheobronchitis.—The term acute obliterative laryngeotracheobronchitis is applied in the present series of 39 cases to an acute nondyptheritic respiratory infection occurring in young children and causing respiratory embarrassment due to obstruction of the respiratory passages. In 37 cases the main pathologic lesion was an obstruction of the small bronchi and terminal bronchioles. Stridor, rhonchi, restlessness, pallor, and cyanosis were the most common physical findings in that order. Chest roentgenograms were generally negative or showed slight emphysema. The leukocyte count was usually normal and throat cultures rarely demonstrated a specific pathogenic organism. Medical therapy consisted of atmospheric humidification, combined with oxygen in the more seriously ill patients, and antibiotics, usually terramycin or chloramphenicol. One death occurred among the medically treated patients. Nine children required tracheotomy; among this group there were 3 deaths. Water-pump suction was found inadequate to aspirate the thick viscid secretions so an electric pump was used instead. The indications for elective tracheotomy were (*1*) cyanosis, (*2*) extreme fatigue, or (*3*) increasing restlessness, pallor, and stridor. The use of this procedure as a last desperate expedient can only bring its performance into disrepute.—*Tracheotomy in acute obliterative laryngeotracheobronchitis, J. N. Briggs & J. R. Heseltine, Brit. M. J., November 15, 1952, No. 4793: 1064.—(E. A. Riley)*

ACTH for Acute Infantile Bronchiolitis.—A study of 19 cases of acute infantile bronchiolitis indicates that corticotropin (ACTH) controls the inflammatory bronchiolar obstruction. These findings are at variance with those reported by some other authors.—*Adrenocorticotrophic hormone in the control of acute infantile bronchiolitis, S. H. Walker, J. Pediat., November, 1952, 41: 528.—(M. J. Small)*

Asphyxia Neonatorum.—The long-term results of treating 66 severely asphyxiated infants with oxygen by endotracheal insufflation are recorded. Following immediate pharyngeal aspiration, those infants who did not breathe immediately were placed head down in a Roberts-Talley infant oxygen rocker. If rocking did not produce respiration within three minutes after birth, a small metal airway was inserted, the infant was rocked, and the pharynx was aspirated under direct vision. After insertion of an endotracheal tube, oxygen was applied at intermittent pressures of about 20 cm. of water. The optimal rate of flow was 1.5 liters per minute. Insufflation was maintained as short a time as possible, the time varying from three to forty minutes but usually in the range of seven minutes. Of the 66 infants, 14 died. Among these, 3 died from causes other than asphyxia, 7 showed an initial response and died later with varying degrees of atelectasis and evidence of amniotic aspiration, and 4 failed to respond to treatment. At the end of

a long-term study of the 52 survivors, 43 appeared normal in every way, 6 were lost to follow-up, and 3 less than three months of age were not developmentally tested.—*Endotracheal insufflation with oxygen in the treatment of asphyxia neonatorum, D. O'Brien & H. Roberts, Brit. M. J., November 1, 1952, No. 4791: 963.—(E. A. Riley)*

Chronic Friedländer Pneumonia in Infancy.—Of 2 siblings with lung disease of several years' duration, one is the only proved case of chronic Friedländer pneumonia reported in an infant. *Klebsiella pneumoniae* were grown in pure culture from bronchoscopic aspirations five weeks after the onset of illness. Almost three years later *K. pneumoniae* and *Staphyloccus aureus* were cultured from a discharging sinus in the lumbo-sacral region. In the second case, though the clinical course and pathologic findings were in keeping with such a diagnosis, no specific etiology was determined, presumably because the extensive use of antibiotics and chemotherapy obscured bacterial investigations. Post-mortem findings in the lungs of both cases resembled the diffuse chronic fibrosis and bronchiectasis described in chronic Friedländer pneumonia in adults.—*Chronic Friedländer pneumonia in infancy, J. Holowach, D. L. Thurston, & H. J. Wohltmann, J. Pediat., October, 1952, 41: 430.—(M. J. Small)*

Bornholm Disease.—Seventeen cases of Bornholm disease were seen, this being the first time that epidemic pleurodynia was observed in Austria. In 6 children the symptoms were those of painful spasms of the diaphragm and of the intercostal muscles accompanied by high fever. In 11 cases, mostly adults, it consisted in spasms of the abdominal musculature. The disease is harmless; administration of analgesics is indicated.—*Bornholmsche Krankheit, R. Lass, Wien. klin. Wchnschr., November 21, 1952, 64: 905.—(G. C. Leiner)*

Herpes and Pneumonia.—During the period from 1933 to 1947, herpes labialis was observed 472 times among 31,940 patients at Sundby Hospital, Copenhagen, Denmark, an incidence of 1.5 per cent. These patients with herpes labialis could be divided into three groups (*1*) 412 with pneumonia, bronchitis, or other pulmonary disease; (*2*) 51 with various infectious diseases excluding pulmonary infections; and (*3*) 9 with dyspeptic affections. Since the great majority of the patients with herpes labialis had pulmonary disease, every febrile patient with herpes should have a thorough examination of the lungs, including a chest roentgenogram. It is an inexplicable fact that pneumonia patients with herpes have a better prognosis than pneumonia patients without herpes.—*Herpes labialis as a complication to medical diseases, with particular regard to the prognosis of pneumonia, O. Sylvest, Acta med. Scandinav., 1951, 141: 385.—(K. T. Bird)*

Torulosis.—A survey chest film of a 30-year-old man revealed a large, round density at the base of the left upper lobe. The patient gave a history of asthma but he was asymptomatic until shortly before he was admitted to a hospital for further examinations. At that time he developed left pleural pain, fever, and dry cough. All examinations carried out at the hospital were noncontributory with the exception of serial roentgenograms which showed an increase in the size of the pulmonary lesion and the development of a pleural effusion. Study of the serosanguineous pleural fluid was not helpful in establishing the diagnosis. At operation, the left upper lobe, which contained a mass measuring 7 by 6 by 6 cm., was removed. The pathologic diagnosis was torulosis. The patient was well without evidence of recurrence four years later.—*Torulosis (cryptococcosis) producing a solitary pulmonary lesion: Report of a four-year cure with lobectomy, M. Berk & B. Gerst, J.A.M.A., August 2, 1952, 149: 1310.—(H. Abeles)*

Acute Blastomycotic Pneumonia.—A 41-year-old white woman had pneumonitis of the right and left lung bases. A sputum smear showed many gram-positive cocci in clusters and many yeasts. Blood culture revealed

Staphyloccus albus. Chemotherapy was ineffective and the patient died after a disease of twenty days' duration. On autopsy *Blastomyces dermatitidis* was found in the lungs, and the diagnosis of fulminating blastomycosis of both lungs was made. *Blastomyces dermatitidis* causes cutaneous and systemic blastomycosis. In this case the infection was primary in the lungs. Stilbamidine may be effective in the treatment of blastomycosis.—*Acute blastomycotic pneumonia: Report of a fatal case of twenty days' duration, R. D. Baker, G. W. Warrick, & R. O. Noojin, A. M. A. Arch. Int. Med., November, 1952, 90: 718.*—(*G. C. Leiner*)

Sarcoidosis with Thrombocytosis.—Symptoms infrequently result from sarcoidosis of the spleen, but may appear with neutropenia, thrombocytopenia, and pancytopenia. In a fatal case of diffuse sarcoidosis complicated by thrombocytopenia and pancytopenia, purpura was secondary to hypersplenism associated with sarcoidosis of the spleen. In previously reported cases of thrombocytopenic purpura secondary to sarcoidosis, thrombocytopenia was reversed by splenectomy. The death of this patient with massive intracranial hemorrhage emphasizes the need for emergency splenectomy once the diagnosis has been established.—*Sarcoidosis with thrombocytopenia: Report of a case, M. H. Edwards, J. A. Wagner, & L. A. M. Krause, Ann. Int. Med., October, 1952, 37: 803.*—(*T. H. Noehren*)

Calciferol for Sarcoidosis.—A series of 24 patients with sarcoidosis of various regions were treated with calciferol. Favorable results were found especially with cutaneous, subcutaneous, and mucosal lesions. The effects of therapy were somewhat less satisfactory with bone and lymph node lesions and even less satisfactory with pulmonary involvement, although some remissions may have been induced in the latter. Toxic reactions due to treatment were observed in more than one-half of the cases. These reactions were occasionally severe but usually transitory nephropathies. It must be emphasized that, although the treatment was interrupted when symptoms of intoxication appeared, delayed signs of renal damage with proteinuria increase in urinary sediment and elevation of the blood nonprotein nitrogen sometimes occurred several days later and persisted for months. In view of these toxic reactions, calciferol treatment is indicated only in chronic, serious cases, especially those with pronounced lesions in the skin and mucous membranes. Calciferol therapy is not indicated in pulmonary involvement alone.—*Treatment of sarcoidosis with calciferol, L. Larsson, A. Liljestrand, & H. Wahlund, Acta med. Scandinav., 1952, 143: 280.*—(*K. T. Bird*)

Corticotropin for Sarcoidosis.—A patient with marked pulmonary sarcoidosis was successfully treated with intensive and prolonged corticotropin (ACTH) therapy. The pulmonary involvement had increased both clinically and roentgenographically during the two years prior to therapy. Corticotropin was given intramuscularly at six-hour intervals; the initial daily dose of 20 mg. was increased at weekly intervals to 80 mg. Subjective improvement was almost immediate. The fever subsided, evidence of pulmonary insufficiency disappeared, and the patient began to gain weight. The spleen became impalpable at the end of the second week. Roentgenographic improvement was minimal during the first three weeks of therapy. During the fourth week, when he was receiving 80 mg. daily and when the circulating eosinophils decreased dramatically, the parenchymal and mediastinal shadows regressed markedly. The signs in the lungs disappeared except for some residual subcrepitant rales at the right base. Because some parenchymal densities persisted and the effectiveness of intravenous administration of the hormone could be evaluated comparatively, treatment was changed to 25 mg. of corticotropin intravenously in 500 cc. of a 5 per cent glucose solution given during eight hours daily. Circulating eosinophils, which had dropped to 55 per cu. mm. on intramuscular therapy, then

fell to 11 per cu. mm. This count was maintained for four weeks. During the last week of intravenous therapy, the daily dose of 25 mg. was infused slowly over a period of twelve hours. There was slight further regression of the pulmonary densities. The mediastinal lymph node enlargement completely disappeared. The minimal residual pulmonary densities probably represented irreversible fibrotic changes in the lung parenchyma. To evaluate the effect of the therapy on lymph node pathology, a node was removed from the right femoral area prior to therapy and showed unmistakable sarcoid changes. Following therapy, the nodes in both femoral regions became impalpable except for one left femoral node which was removed; the extensive hyaline changes and the absence of sarcoid infiltration in it were striking. The smaller doses of corticotropin may have contributed to the ultimate result but the maximal benefit occurred with large intravenous and intramuscular doses. Previous reports that corticotropin therapy is ineffective in sarcoidosis may be explained by inadequate dosage, insufficient duration of therapy, or both.—*Effect of Acthat-c (ACTH) in sarcoidosis, M. A. Miller & H. E. Bass, Ann. Int. Med., October, 1952, 37: 776.—(T. H. Nochren)*

Corticotropin and Bronchial Asthma.—Adrenal cortical function was studied in 10 patients with bronchial asthma. Corticotropin (ACTH) was administered daily in doses of 20 to 40 mg. for at least three days. Following the administration of corticotropin, the changes in the circulating eosinophils and in the urinary excretion of 11-oxysteroids, 17-ketosteroids, and potassium were determined. The eosinophils decreased more than 50 per cent in only 4 of the 10 patients after a single dose of 20 mg. The urinary excretion of 11-oxysteroids increased in only 6 of 8 cases, while the excretion of 17-ketosteroids increased in only 5 of 8 patients examined. The electrolyte hormone was mobilized in 9 patients. The results suggest that a decreased adrenocortical reserve is found quite commonly in patients with bronchial asthma. The disturbance seems to affect primarily the N-hormone and the response of the circulating eosinophils to corticotropin. It is remarkable that a significant response in the excretion of 11-oxysteroids is not always accompanied by a normal fall of the eosinophils. The therapeutic effect was evaluated in those 7 patients who presented severe asthma at the time of study. The response was judged excellent in 3 patients, moderate in 3 patients, and absent in one patient. This last patient, however, responded very favorably to cortisone. There was no apparent correlation between the fall of the eosinophils and the therapeutic response. Thus, eosinophile response cannot be used in the selection of asthmatic patients for corticotropin therapy (Authors' summary).—*ACTH and bronchial asthma: Adrenal cortical function and therapeutic effect, S. Johnsson & B. Skanse, Acta med. Scandinav., 1952, 143: 83.—(K. T. Bird)*

Erythema Nodosum.—Six cases of erythema nodosum in young women were accompanied by bilateral hilar gland enlargement and no other pulmonary changes. All cases occurred between the months of December and May. Resolution was usually complete within six months. It is probable that cases of this nature represent a special syndrome of uncertain etiology as the usual causes were excluded.—*Erythema nodosum with bilateral hilar gland enlargement, a clinical syndrome, L. Dunner & R. Hermon, Brit. M. J., November 13, 1952, No. 4793: 1078.—(E. A. Riley)*

Acute Respiratory Failure in Multiple Sclerosis.—Four patients with clinical courses typical of multiple sclerosis each developed an episode of severe respiratory failure. In 2 instances this was fatal; in the other 2, death was averted by the early use of a Drinker respirator. The patients with respiratory failure had certain distinctive features. Each developed a quadriparesis and depression of thoracic excursions as part of a rapid change in their neurologic status. All 4 were spastic at one time but 2 later became

flaccid; 3 had a segmental level of sensory loss. Treatment with artificial respiration was chosen because the respiratory dysfunction was clearly attributable to ventilatory insufficiency. It was characterized by painless dyspnea, tachypnea, and tachycardia. The expansion of the chest and excursions of the diaphragm were markedly reduced. The vital capacity and arterial oxygen saturation decreased, but cyanosis was observed in only one patient. The early recognition of ventilatory insufficiency depends upon measurements of vital capacity, blood oxygen saturation, and blood carbon dioxide content. They should be used in acute exacerbations of multiple sclerosis and, if indicated, artificial respiration should be begun early. Oxygen inhalation and endotracheal suction were not adequate to prevent death in 2 of the cases. In the 2 survivors, artificial respiration was maintained for sixteen and seven days, respectively. Signs of acute infection, bronchial obstruction, atelectasis, and swallowing difficulties were sought but did not appear. Many fatalities in acute attacks of multiple sclerosis are due to acute ventilatory insufficiency.—*Acute respiratory failure in multiple sclerosis and its management, T. C. Gutherie, J. F. Kurtzke, & L. Berlin, Ann. Int. Med., December, 1952, 37: 1197.*— (*T. H. Nochren*)

Chest in Marfan's Syndrome.—Marfan's syndrome is commonly referred to as arachnodactyly since the most striking sign of this disease is the spider-like appearance of the long, gracile fingers and toes. The clinical manifestations are referable to the involvement of the musculo-skeletal, ocular, and cardiovascular systems as well as to the thoracic cage. The respiratory abnormalities in Marfan's syndrome are primarily referable to either deformities of the thoracic cage or to intrinsic pulmonary or bronchial pathology. In approximately one-half of the cases, thoracic cage deformities such as funnel chest, abnormalities of the ribs, and curvature of the spine are reported. Congenital anomalies of the lungs are also commonly found. Among 3 patients with Marfan's syndrome manifesting thoracic cage, bronchial, and pulmonary abnormalities, one had a funnel chest deformity and bronchiectasis; the second, pulmonary fibrosis and emphysema; and the third, kyphoscoliosis with clinical signs of impaired ventilation. Pulmonary function studies in 2 of these cases indicated decreased vital capacity and maximum breathing capacity, increased ventilatory equivalent, and oxygen unsaturation of arterial blood after exercise. The findings are suggestive of impairment in the diffusion of oxygen across the alveolar membrane.—*Thoracic manifestation in Marfan's syndrome (arachnodactyly), H. Katz, Quart. Bull. Sea View Hosp., April, 1952, 13: 95.*—(*K. T. Bird*)

Emphysema and Ulcer.—A review of a total of 700 consecutive autopsies, all of men, allowed certain groups to be further analyzed as follows: (*1*) 64 patients who had been diagnosed and treated as having chronic pulmonary emphysema and in whom this diagnosis was confirmed at autopsy; (*2*) 36 cases of cancer of the prostate; (*3*) 52 cases of hypertensive cardiovascular disease; and (*4*) 42 cases of bronchogenic cancer. Among the 700 autopsies, were 45 (6.4 per cent) cases of peptic ulcer: 12 (19.0 per cent) in *Group 1*; 2 (5.5 per cent) in *Group 2*; 2 (3.9 per cent) in *Group 3*; and 7 (17.0 per cent) in *Group 4*. In addition to chronic peptic ulceration, some patients had acute peptic ulceration so that multiple ulcers were frequent. Of the 12 patients in *Group 1*, 4 had had severe upper gastrointestinal hemorrhage which contributed to their deaths. Clinical histories were compiled on 72 patients who had been treated for chronic pulmonary emphysema. Of these, there were 14 (19 per cent) on whom a diagnosis of peptic ulcer had been made. This suggests that chronic peptic ulceration occurs more often in patients with chronic pulmonary emphysema than would be expected by chance alone; and that the dyspepsia and epigastric distress which are frequently associated with this chronic pulmonary disease may often be due to peptic ulceration.—*The association of chronic pul-*

monary emphysema with chronic peptic ulceration, P. T. Green & J. C. Dundee, Canad. M. A. J., November, 1952, 67: 438.—(E. A. Riley)

Eosinophilia and Asthma.—Although eosinophilia in the peripheral blood is characteristic of bronchial asthma, hypereosinophilia of more than 15 per cent is relatively rare in adults with bronchial asthma free of complications. In certain instances of bronchial asthma, however, polyneuritic symptoms of pain and numbness develop in the extremities and eosinophilia exceeding 25 per cent is found in the peripheral blood. In 1939, Rachemann and Greene described this syndrome as periarteritis nodosa with bronchial asthma. A 17-year-old woman with polyneuritis in the lower extremities and peripheral eosinophilia ranging from 7.0 to 84.5 per cent has now been observed for more than six years. Eosinophilia and recurrent asthma have persisted, but no biopsy has been performed to fully establish the diagnosis of periarteritis nodosa.—*Eosinophilia and leukocytosis in connection with bronchial asthma, E. Klemola, Acta med. Scandinav., 1952, 144: 119.—(K. T. Bird)*

Prolonged Aerosol Administration.—A reliable, inexpensive apparatus for prolonged continuous aerosol administration consists essentially of a De Vilbiss #40 nebulizer to which is attached a supply bottle and an overflow bottle. Refilling is required only every eight to twelve hours when one-liter bottles are used. This apparatus has been employed primarily for the continuous nebulization of Alevaire, a detergent aerosol solution to dissolve viscid bronchopulmonary secretions. This detergent solution combined a total lack of toxicity with marked activity in lowering surface tension and viscosity. Its uses have included treatment for such conditions as laryngotracheobronchitis, asthmatic bronchitis, bronchiectasis, bronchopneumonia, poliomyelitis with retained secretions due to intercostal or diaphragmatic paralysis, and comatose patients with absent cough reflex. —*Apparatus for prolonged continuous aerosol administration, J. B. Miller, Am. J. Dis. Child., November, 1952, 84: 616.—(M. J. Small)*

Alcohol-Oxygen Vapor Therapy.—Ethyl alcohol was used to treat 50 attacks of pulmonary edema occurring in 45 patients, 40 attacks being acute and 10 subacute. Of the three methods of administration studied, only two were satisfactory. The use of a nasal catheter with 95 per cent alcohol was most suitable for conscious patients and was employed for 36 attacks. A mask used with 30 to 40 per cent alcohol was more convenient with unconscious patients. Ethyl alcohol vapor and oxygen by inhalation were used exclusively for 14 attacks. An excellent result, frequently with dramatic improvement, was noted in 12 (85 per cent). Maximal benefit occurred within an hour. Ethyl alcohol-oxygen vapor was used after failure of conventional therapy in 23 attacks, of which 13 were very severe, 9 severe, and one moderate. Objective improvement occurred in 15, being prompt in 12 of them. Six other attacks responded similarly but a waning effect of previous therapy could not be discounted entirely. The over-all mortality in cases of acute pulmonary edema was 7 deaths among 40 attacks in 35 patients, 5 of whom were clinically relieved of their edema well before death. Of 10 patients with subacute or protracted pulmonary edema treated with ethyl alcohol-oxygen inhalation therapy, improvement was good in 3, moderate in 2, and minimal in 2, while the other 3 failed to improve. Six of these patients died subsequently because of the underlying condition.—*Alcohol-oxygen vapor therapy of pulmonary edema: Results in fifty attacks, M. A. Goldman & A. A. Luisada, Ann. Int. Med., December, 1952, 37: 1221.—(T. H. Noehren)*

Lobar Emphysema in Infancy.—Emphysema confined to one pulmonary lobe was treated successfully by resection of the lobe in each of 5 infants. Etiologically, there was

(*1*) deficient cartilage in the lobar bronchus with excessive infolding of the mucosa causing obstruction in one child; (*2*) a persistent ductus arteriosus extending over the left main stem bronchus in 2 cases, with an anomalous pulmonary artery and bronchi in one of these; and (*3*) no demonstrable bronchial lesion in 2 cases. With lobar emphysema, dyspnea, cyanosis or both appear, without any febrile pulmonary inflammatory process, in a child previously well. Symptoms progress and respond poorly to conservative therapy. Physical examination reveals hyperresonance and diminished breath sound over one hemithorax or over a lobar area with contralateral displacement of heart and mediastinum. In roentgenograms there is a large area of localized radiolucency with a contralateral shift of the heart and mediastinum. The entire radiolucent area has lung markings unlike the area in pneumothorax and single or multiple cysts. Bronchoscopy and bronchography aid mainly in excluding endobronchial obstruction, the most important and frequent cause of which is a foreign body. Exploratory thoracotomy reveals a greatly overdistended emphysematous lobe which does not collapse upon opening the chest. The dyspnea is relieved when the normal lobes are no longer compressed by the emphysematous lobe, prompt recovery without disability follows lobectomy. Symptoms have not recurred and no other lobe has become emphysematous after removal of the affected tissue. All of these cases as well as other reported cases involved the upper and middle lobes.—*Lobar emphysema in infants and children, H. W. Fischer, W. J. Potts, & P. H. Holinger, J. Pediat., October, 1952, 41: 403.—(M. J. Small)*

Streptokinase Treatment.—Intrapleural administration of streptokinase and streptodornase resulted in hyperpyrexia and circulatory collapse in one case. The contents of a serous cavity should be promptly evacuated whenever a febrile response follows the injection of these enzymes. This would prevent any further absorption of toxic products.—*Unusual reaction to intrapleural administration of streptokinase and streptodornase, G. L. Baum & P. Oransky, J.A.M.A., July 12, 1952, 149: 1012.—(H. Abeles)*

Primary Cor Pulmonale.—In primary cor pulmonale there is right-sided cardiac hypertrophy and dilatation without strain on the left heart. To establish this diagnosis it is necessary to exclude cardiac valvular lesions, cardiovascular malformations, chronic pleuropulmonary disease, and specific infections of the pulmonary vessels. Pulmonary vascular sclerosis is the important factor in the development of primary cor pulmonale. Primary cor pulmonale must be considered when a fairly young person with a negative previous history begins to exhibit (*1*) dyspnea, cyanosis, and edema; (*2*) radiologic and electrocardiographic signs of right-sided cardiac strain; and (*3*) accentuation of the pulmonary second sound. In the absence of all known causes of right-sided cardiac strain, including chronic pulmonary disease, mitral valve lesions, and congenital heart disease, the diagnosis may be made by exclusion. The diagnosis may be confirmed by cardiac catheterization, which reveals pulmonary hypertension. It is to be stressed that the cyanosis of cor pulmonale is relatively more marked than the dyspnea in contrast to patients with left heart failure, in whom dyspnea is severe. As a general rule, it may be said that patients with primary cor pulmonale experience no orthopnea and feel well lying flat, unlike patients with left-sided cardiac failure. The prognosis of primary cor pulmonale is serious and the patients follow a progressive and rapid downhill course. Ordinary cardiac therapy appears to be of no avail, particularly in the late stages when the patient has suffered repeated relapses with heart failure. Oxygen therapy has often been beneficial. Morphine is absolutely contraindicated and the utmost care is needed in the use of sedatives.—*Primary cor pulmonale, S. Samuelsson, Acta med. Scandinav., 1952, 142: 177.—(K. T. Bird)*

Self-Induced Foreign Bodies.—Mentally ill patients often swallow foreign bodies or introduce them into body orifices. Such patients may also introduce foreign bodies subcutaneously. During three annual surveys of approximately 45,000 mentally ill patients, foreign bodies were seen in the miniature chest roentgenograms of 28 persons. In 18 of these patients, subcutaneous foreign bodies were found; in all but one, it was a sewing needle, a portion of a needle, or the pointed end of a common pin. Physicians and attendants knew of the practice in only a few cases where infection resulted. In 8 patients intrapulmonary foreign bodies were found; one of them had introduced a needle in the anterior abdominal wall. Of the 8 patients, 6 had a single pin or needle in the right lower lobe, well out in the parenchyma, with no evidence of inflammatory reaction. One patient had a medium-sized, flat-headed screw in the right lower lobe bronchus with considerable pulmonary suppuration and atelectasis of the right lower lobe. One patient had some unidentified metallic foreign body in the right main bronchus with distal lung suppuration. There were 4 patients with foreign bodies, apparently pieces of needles and the pointed part of a safety pin, located in the mediastinum, anterior to the spine. It was supposed that these objects had been swallowed and had perforated the esophagus. Some of these patients were known to have swallowed various foreign bodies. These findings suggest that fraud or deception should be considered in some cases of foreign bodies in the chest.—*Foreign bodies discovered by chest roentgen survey, W. R. Oechsli, Am. J. Roentgenol., November, 1952, 68: 725.*—(*T. H. Noehren*)

Surgery for Lung Abscess.—The results of the surgical treatment of postpneumonic lung abscesses up to the end of 1947 were compared with the results since that time, when antibiotics and resectional surgery have been in use. In the fifteen years prior to 1948, the operative mortality was more than 50 per cent (32 of 62 patients). Postoperative complications were common. Between 1948 and 1951, 103 cases of lung abscesses were seen; in 63 of these, multiple small cavities were present. Thirty-seven patients were treated conservatively, 66 underwent surgery. Pneumotomy was done to drain empyema in 12 patients, 4 of whom died. Resections were done in 54, 8 of whom died. There were 18 pneumonectomies, 31 lobectomies of one or two lobes, and 8 segmental resections. Postoperative empyema occurred in 6 cases, a bronchus fistula in 2. Of the 46 operated patients who are living, 42 are healthy.—*Zur Behandlung der postpneumonischen Lungeneiterungen, O. Steinhardt, Wien. klin. Wchnschr., November 28, 1952, 64: 916.*—(*G. C. Leiner*)

Bronchogenic Cysts.—Among 5 patients operated upon for bronchogenic cysts, 2 had been asymptomatic at the time the lesions were discovered on routine chest roentgenograms. One of these became symptomatic before operation, and the remaining 3 patients also had symptoms referable to the chest. Each of the 5 cysts was resected after aspiration; the 2 intrapulmonary lesions requiring lobectomy, the 3 extrapulmonary cysts were dissected free without sacrificing lung tissue. One cyst in a 44-year-old woman showed histologic changes indicating malignancy.—*Cinq cas de kystes bronchogéniques, F. Roy & J. A. Gravel, Laval méd., November, 1952, 17: 1168.*—(*A. T. Laird*)

Mediastinal Tumors and Cysts.—Between 1933 and 1951, 101 patients with primary tumors or cysts of the mediastinum were observed at the Johns Hopkins Hospital. The largest group of 20 patients had mediastinal tumors of neural origin, classified as ganglioneuroma, neurofibroma, neurinoma, neurogenic sarcoma, or neuroblastoma. All but one of these originated in the posterior mediastinum and 5 were malignant. Mediastinal cysts in 17 patients were classified as bronchogenic, dermoid, enterogenous, pericardial, or nonspecific; 10 were in the anterior mediastinum and 7 in the posterior division. There were 17 patients with thymic tumors; 10 in

the anterior mediastinum and the remainder in the anterior and superior mediastinum. Ten patients had primary undifferentiated carcinoma. All had symptoms, chiefly pain, weight loss, cough, dyspnea, and hoarseness; 2 had superior vena caval obstruction. Four occurred in the anterior, 4 in the superior, and 2 in the posterior mediastinum. In no instance could an origin in the lung be demonstrated. All of the 9 teratomas in this series arose in the anterior mediastinum, were of great size, and were symptomatic; 4 were malignant. Among the 6 patients with primary mediastinal lymphosarcoma, the tumor arose anteriorly in 4 and posteriorly in 2. In only one case was the tumor sufficiently well localized to permit excision. There were 5 patients with the clinical and radiologic manifestations of mediastinal tumor in whom a diagnosis of Hodgkin's disease was ulti mately established by mediastinal exploration. None of these showed clinical evidence that the lymphatic system was involved elsewhere. In all, the mass was in the anterior mediastinum. The tumor could be removed in only one patient. There were 5 patients who had completely intrathoracic goiters; 4 were associated with pain, cough, or dyspnea; and the fifth was found on a routine roentgenogram. Histologic examination of these goiters showed benign adenoma in 3, hyperplasia in one, and carcinoma in one. All of the 5 patients with poorly differentiated sarcomas were young or middle-aged and had clinical manifestations of thoracic disease. The tumor occupied the anterior mediastinum in 3, the posterior in one, and the superior mediastinum in one patient. Although 4 were widely invasive and not resectable, the fifth was well encapsulated and was removed. Histologically, 3 were undifferentiated and 2 were spindle-cell sarcomas. There were 2 parathyroid adenomas, both in the superior mediastinum. These patients had renal calculi and elevated blood calcium and reduced phosphorus levels. Two lipomas were encountered in the posterior mediastinum, one fibroma in the upper posterior mediastinum, one leiomyoma in the posterior mediastinum, and one mesothelioma in the superior mediastinum. Accurate, specific preoperative diagnosis of primary mediastinal tumors was difficult. Symptoms or signs almost never could be related to a specific type of mediastinal tumor. The malignant tumors more often were associated with evidence of rapid growth, constitutional symptoms, and obstructive phenomena but the differences between the benign and malignant group were relatively insignificant. Of the 101 tumors, 60 were benign and 41 malignant. Extensive delay in an effort to establish a specific diagnosis of mediastinal tumor prior to surgical exploration is unwarranted.—*Primary neoplasms and cysts of the mediastinum, D. C. Sabiston, Jr. & H. W. Scott, Jr., Ann. Surg., November, 1952, 136: 777.*—(*M. J. Small*)

Suppurative Mediastinal Dermoid.—In the presence of a mediastinal dermoid cyst, fever and leukocytosis are ominous signs of infection secondary to infection elsewhere, particularly in the respiratory tract. Dermoids may enlarge rapidly following respiratory infections. When a fistula develops between the cyst and the bronchial tree, infection is the rule; in such cases sebaceous material and hair are frequently expectorated and are diagnostic. A dermoid may become infected without a fistulous communication, organisms probably reaching the tumor through the blood stream. Once infection takes place, the prognosis is guarded. Pressure phenomena become greater as the tumor enlarges and adhesions to surrounding structures appear, making surgical removal difficult. The tumor may rupture into neighboring structures with catastrophic results. In the first reported case of myocardial abscesses due to direct extension from a dermoid cyst, the clinical course was the usual one for infected mediastinal dermoids except for cardiac involvement and sudden death. The shadow of the tumor seen on the roentgenogram was first thought to represent an enlarged pulmonary artery. Later, on the basis of fever and a cardiac murmur, subacute bacterial endocarditis

secondary to rheumatic or congenital heart disease was suspected. The patient's death might have been prevented had the mediastinal tumor been diagnosed and surgical treatment instituted earlier. Lindskog and Kausel were correct in that the indication for surgical excision of a presumptively benign mediastinal tumor rests on the demonstration of its existence.—*Abscesses of myocardium due to suppurative mediastinal dermoid: Angiocardiographic and pathologic study, S. R. Rosenbluth, I. Steinberg, & C. T. Dotter, Ann. Int. Med., November, 1952, 37: 1064.—(T. H. Noehren)*

Chylopneumothorax.—A 64-year-old man experienced a sudden, sharp pain while lifting a coal scuttle. The pain was mainly on the right side and was followed by increasing dyspnea. A chest film showed a right pneumothorax. Thoracentesis revealed yellow-white fluid with a specific gravity of 1.020; a smear showed rare erythrocytes and leukocytes. The fluid cleared after the addition of ether, and small globules were found after the fluid was stained with Sudan III. The protein content was 6 mg. per 100 cc.; the fat content was 170 mg. per 100 cc. The fluid was sterile, and a cell block was negative for tumor cells. The fluid absorbed without recurrence. It is assumed that a collateral of the thoracic duct ruptured when the spontaneous pneumothorax occurred.—*Spontaneous chylopneumothorax, report of a case, D. G. Calenda & J. H. Harris, J. A. M. A., July 12, 1952, 149: 1016.—(H. Abeles)*

Solitary Pulmonary Metastasis.—A 28-year-old woman complained of fatigue and slight cough of three weeks' duration. The chest roentgenogram showed a large, circular density in the left upper lobe. A large adenocarcinoma was removed by lobectomy. A year after the operation the patient developed a slight nonproductive cough. A roentgenogram showed a small nodule in the right upper lobe. The nodule enlarged slightly and was removed by a right upper lobectomy fourteen and one-half months after the first lobectomy. The histologic diagnosis was metastasis from the primary growth in the left lung. The patient is living and well five years after the removal of the metastatic lesion.—*Pulmonary resection for metastasis from carcinoma of the lung: Report of a case, A. Lambert, J. A. M. A., August 23, 1952, 149: 1545.—(H. Abeles)*

Bronchogenic Carcinoma.—Bronchogenic carcinoma is now the most frequent malignant disease and, even with treatment, the average length of survival after diagnosis has been short. The average age of 114 patients with bronchogenic carcinoma who were studied was 62.4 years. Of the 114 cases, 93 were considered inoperable and 21 operable but, of these, only 8 proved resectable. In the whole group, the average duration of symptoms before diagnosis was 7.7 months, and the average survival time after diagnosis of the 101 who died was 4.7 months. In the 13 who were operable but not resectable, the average duration of life was 6.7 months after operation, and only one is still alive. In the 8 resectable cases, 3 were still alive at six, twenty-five, and thirty-three months after operation, and 5 had died after an average duration of life of six months. Of the 3 still alive, 2 had recurrences in the operative stump. The only one remaining with a chance of cure was operated on forty-eight months after the onset of symptoms. Frequent examination of sputum for tumor cells might lead to earlier diagnosis and increase the opportunity for operation and possible cure. Sputum examination was a valuable aid in diagnosis in this series, being positive in 47 per cent and positive or suspicious in 60 per cent of the cases in which the examinations were done. Finding a positive sputum is of serious import and does not alter the general outlook. Of the 40 cases in which positive sputa were obtained, only 2 were alive at the time of writing. These 2 were resectable, but one has subsequently developed a recurrence in the operative stump. The prognosis in bronchogenic carcinoma in the group reported was found to be almost invariably fatal and was relatively

unaffected by either earlier diagnosis or treatment.—*Bronchogenic carcinoma, A. J. Blanchard & R. W. Bell-Irving, Canad. M. A. J., November, 1952, 67: 431.—(E. A. Riley)*

Coarctation of Aorta.—Among 18 cases of coarctation of the aorta treated surgically, there was one death from cardiac arrest. The acceptable age limits for the operation are still unknown. One patient, thirty-nine years old, was almost in cardiac failure before the operation and became decompensated after the operation despite excellent lowering of his blood pressure. Another, forty years of age, had relief of headaches and a rise in the blood pressure of the legs, but marked hypertension in the arms persisted. In such cases, functional failure after a successful anatomical correction indicates that the operation was too long delayed and that irreversible changes had occurred. If a child has a rising or greatly elevated blood pressure, the operation cannot be safely delayed but should be done at once. Should future growth result in a relative stenosis at a later age, re-resection may be contemplated. The pathogenesis of the hypertension is not wholly understood. Some experimental work suggests that renal factors may be predominant and this may explain the irreversibility of the hypertension in the older patients. Cardiac arrest is an important operative complication. Early diagnosis and early treatment seem the proper approach to coarctation of the aorta.—*Coarctation of the aorta, F. Glenn & W. D. O'Sullivan, Ann. Surg., November, 1952, 136: 770.—(M. J. Small)*

Endocrines and Aortic Coarctation.—Of 3 female patients with coarctation of the aorta, 2 had Turner's syndrome and one showed delayed puberty. Of 8 male patients with coarctation, 5 showed delayed puberty, while the remaining 3 were normally developed and had no pubertas praecox. In 7 patients the excretion of estrogenic substances, the gonadotropins, and the 17-ketosteroids were examined, with a differential estimation of the 17-ketosteroids. In the majority, the 17-ketosteroid IV was lower than the average normal value, which may point to a low testosterone production. The metabolites of the adrenal cortical hormones were present in relatively large amounts. When autopsied, one patient with Turner's syndrome had macroscopically and microscopically normal thymus and adrenals. The excretion of gonadotropins was increased in one patient with Turner's syndrome. In the male patients with delayed puberty, the excretion of gonadotropins was normal. It is improbable that coarctation of the aorta retarded growth. The same can be said of the thymus and the adrenals. In the patients with endocrine disturbances an increase of QRS (0.12) with M and W configuration was often encountered (Authors' summary).—*Endocrine disturbances in coarctation of the aorta, F. Buchem, B. Homan, E. Dingemanse, & L. Veld, Acta med. Scandinav., 1952, 143: 400.—(K. T. Bird)*

Correction of Interventricular Septal Defects.—Experience with the experimental production and repair of interventricular septa defects in 52 animals shows that a tube pedicle graft of pericardium is reasonably satisfactory for "corking" the opening of defects which are not too large. The defect must be so located that the pericordial "cork" does not block the outflow tract of either the right or left ventricle. In 3 clinical cases, repair of an interventricular septal defect was attempted. In the first, a small high interventricular septal defect produced neither appreciable cardiac enlargement nor symptoms while the patient's activity was severely limited. This patient was in excellent health with no physical restrictions fifteen months postoperatively. The second case as a tetralogy of Fallot with an infundibular obstruction. The patient, 18 years old, had a history of cyanosis since birth, easy fatigability, dyspnea upon exertion, and incapacitating weakness; the heart was slightly enlarged. After successful relief of the pulmonic stenosis by a Brock operation, the septal defect was

repaired, but the graft had to be removed when the patient's condition became precarious due to the narrowing of the right ventricular outflow tract. This patient did well postoperatively, had good relief from the pulmonic stenosis, and became acyanotic. The third patient had a defect approximately the diameter of a finger just beneath the pulmonic valves. Three months postoperatively, this patient was improved but not cured. The septal defect was apparently smaller as judged by the increased intensity of the murmur, and the left to right shunt was decreased with a slight increase in the peripheral arterial oxygen saturation. The technique described seems to be the only method now available, can be performed without great difficulty, and appears to be relatively safe for the patient.—*Experimental and clinical attempts at correction of interventricular septal defects, C. P. Bailey, M. H. Lacy, W. B. Neptune, R. Weller, C. S. Arvanitis, & J. Karasic, Ann. Surg., December, 1952, 136: 919.—(M. J. Small)*

Pulmonary Arteriovenous Fistula.—Asymptomatic arteriovenous fistula was diagnosed in 2 women admitted to the hospital because chest roentgenograms made during a tuberculosis survey had revealed a small rounded shadow in the lung. On fluoroscopic examinations these shadows pulsated, and systolic murmurs were heard over the corresponding regions of the chest. In both patients the fistulas were removed surgically and the patients recovered uneventfully.—*Asymptomatic pulmonary arteriovenous fistula: Report of two cases surgically treated, M. J. Freedman, N. M. Hensler, & B. E. Pollock, Am. Heart J., October, 1952, 44: 594.—(G. C. Leiner)*

Patent Ductus Arteriosus.—Clinical and hemodynamic studies were made on 21 cases of patent ductus arteriosus which, with 2 exceptions, were verified by operation and/or cardiac catheterization. The most prominent clinical sign was the typical systolic-diastolic machinery murmur, loudest in the second and third interspace. This was heard in 18 cases. Three of the 21 patients, all older than eight years, displayed physical signs not characteristic of this condition. Two showed only a faint diastolic murmur to the left of the base of the heart. One showed only a systolic murmur in the second and third interspace at the sternal border. There were 5 patients with a short diastolic and presystolic low-pitched murmur at the apex, characteristic of mitral stenosis. This murmur disappeared in 3 of the 4 patients operated upon. In every case, chest roentgenograms showed dilatation of the pulmonary artery, as a rule in association with signs of increased vascularization of the lungs. Normally, the oxygen content of the blood samples from adjoining chambers of the heart may vary to some extent. However, the difference between the pulmonary artery and the right ventricle, and that between the right ventricle and the right auricle, must be at least 1.2 volumes per cent if importance is to be attached to it. In this series the smallest difference found in any case of persistent ductus arteriosus confirmed by operation was 1.21 volumes per cent. There is considerable variation in the size of the shunt which, in this series, ranged from 1 to 18 liters per minute or from 19 to 72 per cent of the total blood flow through the lungs. In patent ductus arteriosus the electrocardiogram is usually normal, suggesting that the strain on both ventricles is equally great. However, calculation of the mechanical work of the two ventricles shows that the work load is greater for the right ventricle in those cases in which an electrocardiogram shows right heart strain.—*Studies in catheterization of the heart in cases of patent ductus arteriosus Botalli, O. Storstein, S. Humerfelt, O. Müller, & H. Rasmussen, Acta med. Scandinav., 1951, 141: 419.—(K. T. Bird)*

Diaphragmatic Hernia in Infants.—Fifteen congenital diaphragmatic defects occurring in infancy have been repaired by a transthoracic approach. The outstanding symptom was cyanosis; physical and roentgenographic examination confirmed the diagnosis. Three

infants who died postoperatively had associated congenital anomalies, 2 of them incompatible with life. The transthoracic had advantages over the abdominal approach in the repair of diaphragmatic defects in infants. —*Transthoracic repair of diaphragmatic hernia in infants, C. E. Koop & J. Johnson, Ann. Surg., December, 1952, 136: 1007.*—(*M. J. Small*)

Surgical Correction of Funnel Chest.—Nine cases of funnel chest deformity were treated surgically in patients aged eight months to nineteen years. The results in all were excellent and there were no serious complications, residuals, or mortality. Six of the cases were observed for two to four years and there was no indication that recurrence is likely. In one case, scoliosis was remarkably improved coincidentally with correction of the funnel chest deformity. The substernal ligament has not seemed an important factor in these cases. The chief operative complication is tension pneumothorax.—*Surgical correction of funnel chest, F. G. King, Ann. Surg., November, 1952, 136: 798.*—(*M. J. Small*)

Preanesthetic Induced Cough.—The earliest and most constant evidence of tracheobronchial disease is hyperirritability of that tract, as shown by ready, frequent, and prolonged coughing and the presence of secretions. Consequently, the earliest and most reliable sign of tracheobronchial disease should be an abnormal cough when coughing is induced. Induced coughing was used to diagnose preoperative tracheobronchial disease and impending postoperative pulmonary complications in 821 consecutive unselected patients and several hundred selected patients. Each patient coughed voluntarily and forcefully just before anesthesia. Abnormalities of the cough were classified and correlated with other evidence of respiratory disease. A normal cough was a single, brief, bechic blast that sounded "dry" and clear, was not really produced, and was not "self-propagated." An abnormal cough was either "wet" or "dry," depending on the number, degree, and persistence of adventitious sounds after repeated and vigorous coughing. A "dry" cough was considered abnormal if it consisted of paroxysms, hoarse coughing, or was clearly "self-propagated" without a deliberate effort to produce each blast. Patients with a normal induced cough just before anesthesia rarely developed a serious respiratory complication during the first three postoperative days, even after gastric or biliary operations, unless the lower respiratory tract was contaminated with gastric contents. Patients with an abnormal induced cough, particularly if it were "wet," were likely to have a postoperative cough or more serious respiratory complication, especially after an upper abdominal operation. The greatest value of the preanesthetic induced cough was in the diagnosis and selection of the patients who should receive special attention in order to prevent a major postoperative respiratory complication.—*The preanesthetic cough as a method of diagnosis of preoperative bronchitis, B. A. Greene & S. Berkowitz, Ann. Int. Med., October, 1952, 37: 723.*—(*T. H. Noehren*)

Ether Anesthesia, Alveolar Ventilation, and Acid-Base Balance.—Observations were made in patients operated on with ether anesthesia administered through an endotracheal tube by means of a closed circle technique. All intrathoracic procedures were carried out in the lateral position. Serious acidosis due to inadequate alveolar ventilation was always present in unassisted intrapleural operations. The acidosis could be completely prevented by assisting the ventilation. Ventilation had to exceed values considered adequate for normal conscious persons. In all of the patients, manual compression of the anesthesia bag in rhythm with the patient's respiration resulted in ventilation sufficient to prevent carbon dioxide accumulation. No acidosis appeared in the extrathoracic procedures; in fact, a moderate increase in alveolar ventilation and a respiratory alkalosis were often encountered. Ether per se in the fourth

plane, third stage of anesthesia had a stimulating effect upon ventilation and produced mild respiratory alkalosis. At this stage of anesthesia the respiratory center produced a normal ventilatory reponse to increasing carbon dioxide tensions up to 10 mm. of mercury above the resting value; beyond this value the sensitivity of the center to carbon dioxide decreased.—*The effect of ether anesthesia upon alveolar ventilation and acid-base balance in man, J. G. Gabbard, A. Roos, D. E. Eastwood, & T. H. Burford, Ann. Surg., October, 1952, 136: 680.—(M. J. Small)*

Pulmonary Ventilation Studies.—A series of 25 male patients with chronic bronchitis, between the ages of 25 and 63 years, were studied to demonstrate the effect of chronic bronchitis on pulmonary function. Complete case histories and physical examinations were done to exclude any systemic disease which would interfere with pulmonary function; appropriate sensitivity tests were performed to exclude allergic asthma. The cases were divided into 3 groups according to the percentage of total capacity represented by the residual air: *Group 1*, 12 cases in which the residual air constituted less than 40 per cent of the total capacity; *Group 2*, 6 cases in which the residual air constituted more than 40 per cent and less than 50 per cent of the total capacity; and *Group 3*, 7 cases in which the residual air constituted more than 50 per cent of the total capacity. When the residual air constituted more than 40 per cent of the total capacity, a state of hyperinflation existed which might be attended by pulmonary disability. On the basis of available information, all patients with a hyperinflation of more than 50 per cent had associated pulmonary disability. When hyperinflation was attended by pulmonary insufficiency, it seemed probable that structural abnormality, or bronchial or bronchiolar narrowing without structural abnormality was present. In 10 of the 25 cases studied, there was enough hyperinflation to produce pulmonary disability. The age of onset and the duration of disease could not be correlated with the degree of hyperinflation. Low residual air determinations sometimes occurred in disease states in which total lung volume or capacity had been reduced. Such cases, however, still showed an increased ratio of residual air to total capacity. There was good correlation between vital capacity and the ratio of residual air to total capacity. As the vital capacity decreased, the ratio increased; thus, with a cooperative subject, the vital capacity in chronic bronchitis could be used as an index of the ratio of residual air to total capacity. The correlation of the maximum breathing capacity to the increased ratio of residual air to total capacity was almost as good as the correlation of the vital capacity to this ratio. Probable pulmonary disability, as indicated by an increased ratio of residual air to total capacity, was present in all cases in which the maximum breathing capacity was less than 50 per cent of the predicted normal. A reduction in the maximum breathing capacity itself, however, did not necessarily indicate intrinsic pulmonary disease for the results depended also upon coordinated neuromuscular chest movements, a normal thoracic cage, an unobstructed tracheobronchial tree, and normal pulmonary elasticity, as well as the patient's maximal cooperation. The effect of "bronchodilator" and "vasoconstrictor" drugs was tried in 20 cases. In 10, an increase in maximum breathing capacity which ranged from 5 to 66 per cent was observed; in 6 cases the increase was greater than 15 per cent.—*Pulmonary volumina and ventilation studies in chronic bronchitis, I. Karrel & R. Place, Canad. M. A. J., November, 1952, 67: 458.—(E. A. Riley)*

Oxygen Inhalation in Emphysema.—In some patients with pulmonary emphysema, the administration of high concentrations of oxygen results in mental changes ranging from somnolence to coma and sometimes death. The effect of oxygen and carbon dioxide inhalation on the pulmonary ventilation and cerebrospinal fluid pressure of 4 patients with chronic pulmonary emphysema and 3 normal subjects

has been studied in an effort to elucidate the mechanism by which this phenomenon is produced. The inhalation of carbon dioxide by normal subjects increases the cerebrospinal fluid pressure through cerebral vasodilatation. In 2 of the patients with pulmonary emphysema, oxygen inhalation resulted in respiratory depression, carbon dioxide retention, and increased intracranial pressure. Occasional periods of hyperventilation during oxygen therapy will prevent the development of these undesirable effects.—*Increased intracranial pressure in emphysema caused by oxygen inhalation, J. C. Mithoefer, J.A.M.A., July 19, 1952, 149: 1116.—(H. Abeles)*

Altitude Acclimatization.—The rise in erythrocyte count and hematocrit in the early periods after an ascent to high altitudes is due to hemoconcentration and not to an increased number of erythrocytes. An increased or decreased rate in plasma iron turnover and subsequent incorporation of Fe^{59} in erythrocytes is the most sensitive measure yet found for detecting the change in the rate of hematopoietic activity. A change in the rate of erythrocyte production can explain the change in the number and volume of erythrocytes resulting from variations in the oxygen in the inhaled air. It is not necessary to consider a change in the duration of life of the red cell as a mechanism of acclimatization. Altitude polycythemia does not resemble polycythemia vera in that there is no concomitant enlargement of the spleen, thrombocytosis, or leukocytosis. There is no evidence for an increased incidence of polycythemia vera among the Peruvian Indians living at high altitude. Ten days after descent from 14,900 feet to sea level, the iron turnover in the native Peruvian Indian decreased to one-tenth that observed in his native habitat. This approaches that seen in aplastic anemia (Authors' summary).—*A physiological study in the Peruvian Andes, J. Lawrence, R. Huff, W. Siri, L. Wasserman, & T. Hennessy, Acta med. Scandinav., 1952, 142: 117.—(K. T. Bird)*

Cardiac Hypoxemia Test.—The cause of the anginal syndrome is believed to be reduced myocardial oxygen saturation due to coronary arterial insufficiency; attempts have been made by a hypoxemia test to induce objective diagnostic signs. By having the subject inhale a standard gas mixture of 4.5 per cent carbon dioxide, 6.5 per cent oxygen, and 89 per cent nitrogen Malmström rapidly lowered the oxygen tension and saturation of arterial blood. The tension and saturation of the arterial oxygen are consistently reduced because the inhaled carbon dioxide stimulates the respiratory center. Electrocardiograms were obtained before the test and after breathing the standard gas mixture exactly ten minutes with the subject still in hypoxia. Normal values for different age groups were standardized for this test. In general, the average downward displacement of the ST segment by the hypoxemia test was greater in the age group 40 to 50 years than in the age group 20 to 30 years. Although the ST segment deviated much more after the hypoxia test in older than in younger persons, the heart rate increased less in the older subjects. This implies that the ST depressions are not due to relative tachycardia but to the induced anoxemia. None of the normal subjects displayed T wave abnormalities.—*The cardiac hypoxemia test (CO_2, O_2), its accuracy and normal variability, T. Sundin, Acta med. Scandinav., 1952, 142: 82.—(K. T. Bird)*

Venous Pressure Measurement.—A new method of making direct venous pressure measurements uses the Tybjaerg Hansen electric condenser manometer. The apparatus is easily portable and its advantages over the simpler methods are, other than greater accuracy, that a true curve can be recorded without any distortion in phase or amplitude, that fine needles with an outside diameter of 0.4 to 0.5 mm. may be employed, and that the measurement may be carried out continuously for hours. Simultaneous measurements with a blood-filled glass tube showed fairly good agreement between the results of both methods in most, but not all, of 38 cases. In 40 normal adults a venous pressure between 70 and 106 mm. of water, averaging 88 mm., was found (Authors' summary).—*Venous pres-*

sure measurement: II. A new technique for direct venous pressure measurement using an electric condenser manometer, A. Pedersen & J. Husby, Acta med. Scandinav., 1951, 141: 317.—(K. T. Bird)

Water-Soluble Contrast Media for Bronchography.—Bronchography with a water-soluble medium, ioduron B, consisting of a mixture of 50 per cent ioduron (diethanolamine salt of diiodopyridon-N-acetic acid) and approximately 2.5 per cent water-soluble cellulose (sodium salt of the glycolic acid ether of cellulose) was performed sixteen times on 15 patients. All of the patients were followed longer than six months following bronchography or until death. In none was there any clinical or radiographic damage that could be ascribed to ioduron B. Six patients had resection of a portion of lung and no pathologic changes could be attributed to the bronchographic medium. It was found that the water-soluble contrast medium required greater quantities of cocaine to obtain satisfactory levels of local anesthesia. Even with 25 cc. of 4 per cent cocaine and examination of only one side, the medium was still more liable to provoke reflex cough then oily contrast substances; this was its main drawback. For this reason it is not considered a safe agent for use in performing bilateral bronchography at one sitting. In most instances the contrast medium disappeared from the bronchial tree within one to three hours, permitting bronchographic re-examination within a relatively short time. Since the effect of retained cellulose compound in the lung is a subject of controversy, animal experiments were carried out with a 5 per cent solution of unhydrolyzed dextran mixed with 50 per cent Diodrast. In preliminary dog experiments this proved to be satisfactory for bronchography. Ioduron B seems well suited for use in those patients in whom bronchography may be confined to a limited number of pulmonary segments, particularly in those pathologic states in which partial obstruction of the bronchial passages enhances retention of oily media. In those patients in whom a survey bronchogram of both lungs is required, iodized oils still possess many desirable qualities which outweigh their disadvantages. *—The use of water-soluble contrast media for bronchography, J. V. Rogers, Jr. & H. S. Weens, Ann. Surg., December, 1952, 136: 971.—(M. J. Small)*

ANTIMICROBIAL THERAPY

Isoniazid in Tuberculous Diabetics.—The administration of isoniazid to tuberculous diabetic patients was approached with caution since this drug caused a rapid and decided increase in appetite and weight. Such changes have usually been associated with a loss of carbohydrate tolerance by the diabetic. Accordingly, 10 diabetic patients who were receiving isoniazid for tuberculosis were observed for four months to determine the effect of the drug on the diabetes. The carbohydrate intake of these patients was increased on an average by 29 gm. a day. The changes in the protein and fat content of the diet were negligible. The total caloric intake increased 8 per cent. The insulin requirement rose from an average of 31 units of protamine zinc insulin daily to an average of 43.5 units daily. Nevertheless, each unit of protamine zinc insulin covered more carbohydrate than before the institution of therapy. The average weight gain in the four-month period was 14.3 pounds.—*Isonicotinic acid hydrazide in the tuberculous diabetic: A preliminary report, A. R. Spiegelman & T. J. Quigley, Quart. Bull. Sea View Hosp., October, 1952, 13: 203.—(K. T. Bird)*

Allergy to Isoniazid.—A pharmacist developed an acute vesicular confluent dermatitis upon contact with isoniazid. Patch tests were done with all chemicals the patient had worked with prior to the onset of the dermatitis and with the filler and binders of the isoniazid tablets. All the patch tests showed no reaction except for the one containing isoniazid. The dermatitis has gradually subsided since discontinuance of work and avoidance of contact with isoniazid.—*Cutaneous al-*

*lergy from local contact with isonicotinic acid hydrazide, J. W. Jordon, J.A.M.A., August 2, 1952, **149:** 1316.—(H. Abeles)*

Deaths Due to Streptomycin Enhancement.—In 7 cases of chronic tuberculosis, treatment with streptomycin was, at first, followed by general improvement, but shortly thereafter by rapid progression of the pulmonary lesions and death. All 7 strains of tubercle bacilli were, not only resistant to streptomycin, but grew better in presence of the drug. These bacilli may be able to use streptomycin as a nutrient. Streptomycin-dependent bacilli may be present together with normal strains before treatment or may be secondarily introduced by reinfection during the sanatorium stay, the strains originating from persons already treated with the drug.—*Alcuni quadri clinico-radiologici di streptomicino-resistenza e streptomicino-incitabilità, A. Cimino, Ann. Ist. Carlo Forlanini, 1952, **13:** 355.—(A. Mochi)*

PAS Therapy.—The best clinical and roentgenographic results are achieved when *p*-aminosalicylic acid (PAS) blood concentrations are in the neighborhood of 60 mg. per 1,000 ml. Combined oral and intravenous administration was best suited to obtain optimal blood levels for eight hours. A total daily dose of 22.5 gm. of sodium PAS was distributed in such a way that the oral dose was given three hours after the end of the intravenous infusion. Various brands of PAS for oral use were investigated; the most active and best tolerated product was an association of sodium PAS and pectin enriched with vitamin C and certain flavone derivatives extracted from orange rind. No gastrointestinal disturbances were observed with this mode of administration and the results were remarkable.—*Étude clinique et experimentale d'un PAS retard, "L'interêt de son association aux perfusions de PAS," A. Duroux, R. Verges-Breton, & J. Desbordes, Presse méd., September 24, 1952, **60:** 1256.—(V. Leites)*

Allergy to PAS.—Severe sensitivity reactions to *p*-aminosalicylic acid (PAS) were observed in 2 cases three to four weeks after the beginning of the treatment. After the sensitivity to PAS had been established, resumption of the treatment was followed by severe anaphylactic reaction with high fever, exanthema, desquamation, peripheral lymph node enlargement, angioneurotic edema, asthmatic manifestations, diarrhea, peripheral collapse, and hemorrhage. There was marked leukocytosis with increase of the lymphocytes and eosinophils. In view of the possibility of such complications, it is important to study the allergic history of each patient before PAS treatment is instituted.—*Schwere allergische Reaktionen gegen p-Aminosalizylsäure, W. Kniest, Deutsche med. Wchnschr., May 23, 1952, No. 21: 676.—(L. Molnar)*

Febrile Reactions to PAS.—During the years 1950 and 1951, 590 patients in the Royal Edward Laurentian Hospital were given courses of *p*-aminosalicylic acid (PAS), with or without concomitant streptomycin therapy. The incidence of febrile reactions to PAS was approximately 1 per cent. The patients were given PAS in doses of 10 to 15 gm. in three divided daily doses. Febrile reactions to PAS in the 6 patients occurred thirteen to thirty-seven days after therapy was started. Occasionally this febrile response was associated with an erythematous skin reaction. Administration of even small quantities of PAS to patients who had once responded with a febrile reaction regularly evoked a prompt rise in temperature, sometimes with skin manifestations. These observations indicate that tissue sensitization plays an important part in febrile reactions due to PAS.—*Febrile reactions to PAS, J. C. C. Yeh, Canad. M. A. J., November, 1952, **67:** 431.—(E. A. Riley)*

Hypothyroidism Due to Amithiozone.—During treatment of patients suffering from pulmonary tuberculosis with dihydrostreptomycin, *p*-aminosalicylic acid (PAS), and amithiozone, thyroid enlargement was ob-

served in 4 of 54 patients, 2 of whom had concomitant hypothyroid symptoms. One of the latter patients died in a state of hallucinosis and mental confusion with signs of cerebral edema. In addition to cerebral edema with degenerative changes of the ganglion cells, the autopsy revealed marked thyroid changes similar to those seen following thiouracil therapy. The cerebral changes were identical with those described after treatment with amithiozone alone; the changes observed in this case should therefore be ascribed to this drug. Due to the chemical relation of amithiozone with the thiourea compounds and the antithyroid effect of the drug demonstrated in earlier experiments on animals, amithiozone must be held responsible also for the changes in the thyroid and its functions. According to recent findings, however, PAS also has an antithyroid effect and there may be a synergistic effect of the two drugs. The cerebral changes observed in this fatal case might have been caused by hypothyroidism due to amithiozone. Although such a mechanism has not been proved, this possibility should be considered in cases of cerebral complications following amithiozone medication (Authors' summary).—*Hypothyroidism and cerebral edema following combined treatment of tuberculosis with Conteben (TB I 698) and p-aminosalicylic acid, N. Bergqvist & O. De Maré, Acta med. Scandinav., 1952, 143: 325.—(K. T. Bird)*

Studies on Streptomycin Resistance.—Tubercle bacilli isolated from different organs of the same patient vary considerably in their streptomycin resistance. Bacillary resistance is highest in sputum and progressively less in cavitary secretions, pericavitary, splenic, hepatic, and renal lesions. Resistance varies both in frequency of resistant organisms and in the degree of resistance shown by the bacilli. It is generally believed that bacilli spread from a common source, usually a pulmonary cavity; the variations in sensitivity must be due to unknown factors present in some of the organs and able to inhibit development of streptomycin-resistant strains. To obtain confirmation of this theory, two comparable groups of 30 guinea pigs each were infected with two streptomycin-resistant and one sensitive strain, alternately, in the lungs and in the kidneys. Fifteen days after infection, one-half of the animals in each group were treated with streptomycin; at the end of sixty days, all of the animals were sacrificed and cultures were made of the various organs. Injection of resistant bacilli into the kidneys produced the severe, generalized tuberculosis commonly seen in infected guinea pigs, but the kidneys themselves contained only circumscribed, small lesions. Few colonies were cultured from the kidneys; most grew from the liver and spleen fragments. Organisms from the lungs, spleen, and liver were most streptomycin-resistant, while those from the kidneys were definitely less resistant. Animals infected with streptomycin-sensitive bacilli developed only small, circumscribed lesions, if they were treated with streptomycin, or generalized tuberculosis, if not treated. Only a few resistant strains were obtained from cultures of lung tissue. When the tubercle bacilli had been injected into the lungs instead of the kidneys, they maintained their resistance to sterptomycin and even increased it slightly in some cases. Thus, resistance to streptomycin develops in different ways according to the organs in which the bacilli are located, whether the focus is primary or secondary.—*Rene e streptomicino-resistenza dei bacilli di Koch, G. Daddi, M. Lucchesi, & L. Sprovieri, Ann. Ist. Carlo Forlanini, 1951, 13: 265.—(A. Mochi)*

Sensitivity Studies.—The sensitivity of a strain of tubercle bacilli to antimicrobial drugs may vary when different culture media are used. To study the influence of media on results of sensitivity determinations, the Dubos liquid medium with Tween and albumin and the Youmans medium with beef serum were compared with Jensen's modification of the Löwenstein solid medium. Sensitivity to streptomycin did not vary notably among these three media. In determining sensitivity to para-aminosalicylic acid (PAS),

however, the quantity of inoculum was important, and titration became illusory or impossible in liquid media if the inoculum exceeded 0.01 mg. of living bacilli per 5 ml. of culture medium. The effect of inoculum size was negligible on solid medium. After inoculation of 0.01 mg. in liquid medium, 10 per cent of the strains were aberrant and exceeded the usual bacteriostatic levels. On solid medium, there were no aberrant strains. Simultaneous studies of sensitivity to PAS using the same strains in equal concentrations with liquid and solid media showed normal sensitivity on solid medium, while the strains appeared to be resistant or aberrant in liquid medium. Aberrant results of titration in liquid medium occurred also for amithiozone and isoniazid. A solid medium should be used, therefore, to determine sensitivity to antimicrobial drugs. Selection is not the only factor responsible for variations of sensitivity in liquid medium and the role of extrinsic factors should be further investigated.—*Variations de la sensibilité de Mycobacterium tuberculosis aux antibiotiques en milieux de culture liquides, P. J. Coletsos, Ann. Inst. Pasteur, October, 1952, 83: 491.—(V. Leites)*

Nystatin, a Coccidioidocidal Antibiotic.—*In vitro* nystatin, an antibiotic from an actinomycete of the genus of *Streptomyces*, completely inhibited the growth of *Coccidioides immitis* on Sabouraud's medium in a concentration of 7.5 γ per ml. Propylene glycol was utilized as a solvent for the nystatin since it was itself mildly antifungal and also could be taken orally and intravenously with relatively no toxic effects.—*Nystatin: A coccidioidocidal antibiotic, R. Cohen & P. A. Webb, Arch. Pediat., October, 1952, 69: 414.—(M. J. Small)*

Terramycin for Childhood Pneumonia.—A consecutive series of 50 children with pneumonia were divided alternately into two groups of 25, one for treatment with terramycin, and one for the standard treatment with penicillin and sulfonamide. Within each group there was an equal division between lobar and bronchopneumonias. The average age was 3.2 years in the terramycin group and 2.1 years in the standard group. Thirteen in the terramycin group and 11 in the standard group had histories of previous chest infection. The average duration of illness before treatment was slightly higher in the standard group, as was the average temperature on admission (102.7°F.). The terramycin group received terramycin orally, 20 mg. per pound (44 mg. per kg. of body weight) per day in 4 doses. The standard-treatment group was given 0.5 gm. of sulfadimidine orally every four hours and 300,000 units of procaine penicillin intramuscularly at twelve-hour intervals if the patients were more than three years old. If less than three years, 0.5 gm. of sulfadimidine was given immediately and 0.25 gm. every four hours, with 150,000 units of procaine penicillin G every twelve hours. Treatment was continued until the clinical condition was satisfactory and the temperature had been normal for forty-eight hours. The effectiveness of treatment was assessed by the duration of fever, the average stay in the hospital, the development of complications, and the mortality. There was no significant difference between the two groups in the duration of pyrexia (3.0 and 3.0 days) nor the length of stay in the hospital (9.9 and 10 days). There was one death in the standard group which occurred in a Mongol eight months of age who succumbed within three hours of admission. In the terramycin group there were 8 instances of delayed pulmonary resolution as compared with 2 in the standard group. A thrush infection of the mouth developed in 4 of the terramycin group. In view of the comparability of the two groups, there was no evidence that terramycin is more effective than the standard treatment. The drug did, however, avoid the unpleasantness of giving injections to children and the possibility of toxic renal or hematological effects of sulfonamide, although none were observed in this series. From the results obtained in this trial, and on account of the expense and limited availability of terramycin, it is suggested that

penicillin and sulfonamide remain the most satisfactory treatment for pneumonia in children.—*Terramycin in the treatment of pneumonia in children, O. D. Fisher & C. R. Whitfield, Brit. M. J., October 18, 1952, No. 4798: 864.—(E. A. Riley)*

LABORATORY STUDIES

Enzymic and Lipid Histochemistry of Tuberculosis.—Mice, rats, guinea pigs, and rabbits were inoculated with the Vallée strain of bovine *M. tuberculosis* and were killed 13, 18, 31, 39, 53, and 59 days after injection. The lesions in lung, liver, and spleen were studied by histochemical methods for enzymes and lipids. Acid phosphatase was shown to be the most important single enzyme, being present in large amounts in the mononuclear phagocytes of resistant animals such as the mouse and rat. In the more susceptible animals, such as rabbits and guinea pigs, no acid phosphatase was found in the mononuclear cells, but large amounts of this enzyme were found in the necrotic lesions. Since extracellular enzymes were never found in the lesions of resistant animals, the spread of tuberculosis in susceptible animals may be due to proteolytic or other enzymes derived from dead polymorphonuclear leukocytes. The distribution and activity of acid and alkaline phosphatase and esterase in the tuberculous lesions of guinea pigs were unaltered by treatment with streptomycin or isoniazid. The phosphatides of tubercle bacilli may be one substrate for the acid phosphatase of the mononuclear phagocytes, and it is supposed that the enzymic armament of these cells is a contributory factor in the mechanism of natural resistance to tuberculosis.—*The enzymic and lipid histochemistry of experimental tuberculosis, E. Gragg & A. G. E. Pearse, Brit. J. Exper. Path., December, 1952, 33: 567.—(H. J. Henderson)*

Experimental Tuberculosis.—Tuberculin allergy occurs earlier in guinea pigs after inoculation into the lymph nodes than after subcutaneous injection. Twenty guinea pigs were injected with various dilutions of a virulent strain in Dubos medium into the cervical and inguinal lymph nodes and showed tuberculin conversion eight to twelve days later. The reactions were intense and frequently ulcerative, persisting during the entire survival period; the tuberculin allergy was resistant to all attempts at desensitization. —*Tuberculose du cobaye par inoculation intraganglionnaire: Étude de l'allergie, P. Gastinel & Y. Coutel, Ann Inst. Pasteur, September, 1952, 83: 393.—(V. Leites)*

Focal Tuberculoid Lesions in Serum Sickness.—In man, tuberculoid lesions occur in association with the necrotizing inflammatory arterial lesions produced by anaphylactic hypersensitivity. To study this phenomenon, anaphylactic reactions of the serum sickness type were produced in rabbits by a single intravenous injection of sterile horse serum, 10 cc. per kg. of body weight. Some of this antigen remained in the circulation until, and even after, antibody appeared. When the animals were killed twelve to sixteen days after injection, pronounced tuberculoid lesions were found only in the spleen; loose collections and occasional coherent aggregates of epithelioid cells were noted in some lymph nodes. Approximately one-half of the 60 rabbits injected showed tuberculoid lesions, 60 per cent had glomerulonephritis, and approximately 70 per cent had periarteritis nodosa. There was no significant correlation between the development or degree of anaphylactic tuberculoid lesions and the cardiovascular or renal lesions. Nor was there any close correlation between the development of the tuberculoid lesions and the antibody titer or degree of skin hypersensitivity. It seems that an individual "disposition" governs the type of lesion that the hypersensitive body will develop in response to a given antigen. The exact pathogenesis of the tuberculoid lesions is not clear. In man the tuberculoid reaction often appears to be incited by altered collagen, yet in both men and experimental animals tuberculoid reactions may occur where there is no primary collagen degeneration. While one antigen may be more effective than another in

inducing a hypersensitive tuberculoid reaction, different individuals do differ in their tendency to react in this manner.—*The occurrence of focal tuberculoid lesions in experimental serum sickness, A. R. Rich, Bull. Johns Hopkins Hosp., August, 1952, 91: 109.—(J. S. Woolley)*

Stain for Tubercle Bacilli.—The acid-fast staining of tubercle bacilli is improved by (*1*) decreasing the concentration of ethanol and in preparing the stock solution of fuchsin, (*2*) using soluble starch as a hydrophilic colloid to protect carbofuchsin, (*3*) substituting an organic for a mineral acid as the decolorizing agent, and (*4*) employing trypoflavine as a counterstain. The reagents consist of (*a*) the stain made by mixing, after separate filtration, 1.1 gm. of basic fuchsin in 20 cc. of ethanol and 80 cc. of 4 per cent carbol in 10 cc. of 0.1 per cent boiled soluble starch; (*b*) the decolorizing solution of 60 cc. of 20 per cent aqueous sulfo-salicylic acid with 40 cc. of acetone, to be stored in a brown bottle; and (*c*) the counterstain which consists of 10 cc. of neutral formalin, previously shaken with powdered calcium carbonate, 10 cc. of formalin, 4 cc. of 0.5 per cent tryptaflavine (intravenous) solution, and 20 cc. of distilled water. In preparing the stain, the concentration of ethanol should be low enough to allow turbidity to appear when the fuchsin and carbol solutions are mixed; this often is as low a concentration as 30 per cent ethanol. If overstaining becomes evident, the stain should be filtered after heating to 60°C. and cooling. The staining is carried out either by a "hot" or a "cold" method. In the former, a fixed smear is heated for thirty seconds or more while flooded with the stain; after standing for five minutes it is washed, decolorized, and washed again; it is then counterstained for one minute and washed before drying by heating. The counterstaining may be omitted. In the "cold" method, the stain is used for fifteen to thirty minutes without heating. The use of these techniques has increased by 10 per cent the proportion of sputa found to contain tubercle bacilli.—*A new staining method for tubercle bacilli (Japanese), O. Kuroda, J. Japan M. A., September 15, 1952, 28: 282.—(L. B. Hobson)*

Culture of Tubercle Bacilli.—Since it appears necessary to employ both glycerolated and glycerol-free media in the cultivation of tubercle bacilli from sputum, Dorset egg medium without glycerol, Corper-Cohn medium with and without glycerol, and Löwenstein-Jensen medium with and without glycerol were tested in two trials, each involving 2,000 specimens, in an attempt to determine which glycerol-free medium could best be used alone or in conjunction with a glycerolated medium to give the maximum isolation of tubercle bacilli. The egg-yolk medium of Corper and Cohn was not found to be significantly inferior to Löwenstein-Jensen medium with glycerol in positive isolations but took longer to produce them. The most satisfactory combination appeared to be these two media. Dorset egg medium was least satisfactory but there was little to choose between the other two (Author's summary).—*The use of Dorset, Corper-Cohn and Löwenstein-Jensen media in the diagnostic culture of Mycobacterium tuberculosis, C. Collins, Acta tuberc. Scandinav., 1952, 27: 66.—(K. T. Bird)*

Culture of Tubercle Bacilli.—On good nutrient media, mammalian tubercle bacilli are capable of growing at various temperatures from an optimum of approximately 37° C. to an upper limit of approximately 42° C. and a lower limit of approximately 27° C. Although growth occurs relatively rapidly in the upper ranges of temperature of incubation, it may require as long as one year for visible growth to become evident at the lowest level of temperature. The avian tubercle bacilli have a much wider temperature range for growth on a good nutrient medium than the mammalian bacilli and also show a comparatively speedier rate of development. At the lowest temperature limit of growth, the egg-yolk medium proved more efficient as a nutrient for mammalian tubercle bacilli

by yielding a greater and more prolific growth earlier when compared with other commonly used egg media, a feature which is not disclosed at optimum incubation temperature (37° C.) (Author's summary).—*The growth of tubercle bacilli at sub-optimum temperature, H. J. Corper, Acta tuberc. Scandinav., 1952, 26: 96.*—(*K. T. Bird*)

Diagnostic Cultures and Inoculations.—During a two-year study tubercle bacilli were demonstrated by cultures in 32 per cent of cases in which they were not found by examining smears. The cultures were considered negative only after two months of incubation. Receiving the specimens in bottles containing a solution of trisodium phosphate reduced the incidence of contaminated cultures to approximately 2.5 per cent. The phosphate solution destroyed only a small number of bacilli after several days of contact but it delayed the appearance of colonies for several days. Cultures were especially valuable in examining urine, which may contain acid-fast bacilli other than *M. tuberculosis*. Among 800 specimens, tubercle bacilli were recovered in 144 cases by both culture and guinea pig inoculation, in 44 cases by animal inoculation alone, and in 38 cases by cultures before animal inoculations became positive.—*Diagnostic bacteriologique de la tuberculose, G. Bray & N. Kariger-London, Acta tuberc. belg., August, 1952, 43: 323.*—(*A. T. Laird*)

Resistance to Tuberculosis.—Methylic antigen is a methyl alcohol extract of dry acetone-extracted tubercle bacilli with a final strength corresponding to 10 mg. of bacilli per cc. Repeated injections of 5 cc. into guinea pigs or rabbits have produced marked resistance to experimental tuberculosis two weeks after the last injection. This antituberculous resistance was not accompanied by the development of tuberculin allergy. In the present study the duration of protection against experimental tuberculosis as well as the relationship to BCG vaccination was investigated in the following experiments: (*1*) Two months after 6 guinea pigs received four subcutaneous injections of methyl antigen, they were infected with a virulent human strain (572 H). The average number of tuberculous lesions per animal was 40 as compared with 100 in untreated controls. (*2*) Another 20 guinea pigs were given methylic antigen in the same manner but infection with 572 H was delayed until four months later. No difference in character and extent of experimental tuberculosis could be demonstrated between treated animals and controls. (*3* and *4*) Rabbits, given methyl antigen and infected with bovine bacilli two months later, had an average of 80 lesions in animals which received antigen intravenously and 60 in those given antigen subcutaneously. The average number of lesions was 100 in the controls. (*5*) A group of 12 guinea pigs was vaccinated with 10 mg. of BCG each, another group of 12 received five injections of methyl antigen, and a third group had BCG vaccination followed by injections of methyl antigen. Untreated controls showed an average of 89 lesions per animal; the number was 16 in the BCG group, 16 in the methyl antigen group, and 7 in the group treated with BCG and methyl antigen. The latter group showed the largest proportion of animals without any demonstrable tuberculous lesions in the organs. (*6*) Rabbits also demonstrated the superiority of the combined use of BCG and methyl antigen. It is concluded that antituberculous resistance after methyl antigen is of shorter duration than that produced by BCG although it develops earlier. The experiments with methyl antigen prove that immunity can be dissociated from allergy.—*Résistance antituberculeuse sans allergie conférée aux animaux de laboratoire par l'antigene méthylique. Étude de sa durée et de l'action préventive de ce produit associée a celle du BCG, L. Nègre, Ann. Inst. Pasteur, October, 1952, 83: 429.*—(*V. Leites*)

Antituberculous Vaccination. — Seventeen dogs were vaccinated at birth with BCG and 16 others with preparations from dead tubercle bacilli: "*anatuberculine integrale*" of Petrag-

nani (AIP), "vaccination Petragnani-Salvioli" (VPS), and "diffusion vaccine" of Salvioli (VDS). After fifty to eighty days the dogs were infected with virulent tubercle bacilli by the intravenous route. All unvaccinated controls died of tuberculosis within four months after infection. The mortality was 14.2 per cent in the BCG-vaccinated group and 8.3 per cent in the groups vaccinated with dead bacilli. All controls showed grave and extensive parenchymal lesions, while in the BCG-vaccinated animals there was a notable percentage of benign changes: 34.7 per cent had fibrous lesions, 58.8 per cent had productive nodules, and 5.8 per cent had allergic foci. Benign lesions were even more frequent in the animals vaccinated with dead bacilli: fibrosis in 46.1 per cent of the dogs, productive lesions in 84.6 per cent, allergic foci in 15.3 per cent, whereas grave tuberculous lesions, such as tuberculous bronchopneumonia, were seen in only 15.3 per cent. Tuberculous involvement of tracheobronchial lymph nodes was constant in the controls; it was found in 37.5 per cent of the BCG-vaccinated animals, and in 15.4 per cent of those vaccinated with dead bacilli.—*Resistance à la tuberculose chez les chiens vaccinés par le BCG et par des germes morts, G. Salvioli, A. Degli Espositi, & A. M. Dina, Pressa méd., November 8, 1952, 60: 1508.*—(*V. Leites*)

Vole Bacillus Vaccination.—Numerous experimental and clinical investigations have established that BCG possesses the properties necessary to act as a vaccine. The vole bacillus may also confer immunity to tuberculosis in guinea pigs and in humans. Since previous investigations have not clearly shown which of the two is preferable, it appeared desirable to possess a more accurate knowledge of the comparative immunizing properties of the vole bacillus and BCG. Accordingly, studies were done which revealed that vaccinations of guinea pigs with vole bacilli and with BCG both inoculated subcutaneously in doses of 10 mg. result in the same degree of immunity. Thus, vaccination with vole bacilli does not appear to be superior to BCG vaccination.—*On vaccination with vole bacilli, P. Moller, Acta tuberc. Scandinav., 1952, 26: 163.*—(*K. T. Bird*)

Hemagglutination Reaction in Tuberculosis.—The hemagglutination reaction of Middlebrook and Dubos was simplified by using human type O erythrocytes, which in the study of human sera avoids difficulties with anti-sheep-cell agglutinins, and by using different antigens. The original aqueous extracts were too complex to prepare; a new tuberculin prepared with benzoic acid (I. P. 48) was shown to be very specific and was used instead. The hemagglutination reaction gave 93 per cent negative reactions in human subjects free from tuberculosis and 79 per cent positive reactions in tuberculous subjects. It was independent of the allergic state and often appeared earlier than the cutaneous reaction to tuberculin. It could be used as a diagnostic test in animals. Vaccination with BCG caused in man a brief humoral modification but, in animals, a constant and prolonged one. Hemagglutination appeared to be more sensitive and more specific than complement deviation. It gave cross-reactions, however, so that infections caused by the various human and bovine types of tubercle bacilli could not be distinguished. The sensitivity of the reaction depended upon the quality of the antigen employed (Authors' summary).—*La réaction d'hémagglutination dans la tuberculose, C. Gernez-Rieux & A. Tacquet, Ann. Inst. Pasteur (Lille), 1950, 3: 1.*—(*F. S. Lansdown*)

Hemagglutination and Conditioned Hemolysis.—In several animal species, experimental tuberculosis caused antibodies to appear consistently. Conditioned hemolysis was generally more sensitive than hemagglutination in detecting these antibodies. As the infection regressed under the influence of antibiotics, the antibody titer decreased and rose again as the remaining living tubercle bacilli reinvaded the animal. The antibody titer was unrelated to immunity, and absence of anti-

bodies was not a sign of definitive cure. In clinical tuberculosis, the value of these reactions was seen in the different localizations and forms of pulmonary tuberculosis. In a study of more than 3,000 sera, titers of 1:16 or higher were adopted as indicative of active tuberculosis in adults. This titer, however, varied with the antigen used. With tuberculin I. P. 48, hemagglutination reactions were negative in 90.9 per cent of nontuberculous subjects and positive in 61.3 per cent of tuberculous subjects. The hemolytic reaction with the same antigen gave 87.9 per cent negative reactions in healthy subjects and 82.4 per cent positive reactions in tuberculous subjects. The results of the two reactions were not always superimposable and it was valuable to perform them conjointly. Hemagglutination and hemolysis reactions were more specific in children than in adults. With the antigen I. P. 48, a titer of 1:8 was the limit of positivity for children and in 95.7 per cent of the nontuberculous subjects, hemagglutination was negative; in 96.9 per cent of the tuberculous children, hemagglutination was positive, as was hemolysis in 91.9 per cent. Clinical observations, particularly after treatment with antibiotics or excision, gave no evidence of any prognostic value of antibody titers. There was no relation between hemagglutination and the erythrocyte sedimentation rate, deviation of complement, or the Vernes reaction. Better antigens and techniques may make these reactions more valuable and a trial of conglutination seems warranted. Several different antibodies certainly are demonstrable in tuberculous serum.—*Les réactions d'hémagglutination et d'hémolyse conditionnée dans la tuberculose, C. Gernez-Rieux & A. Tacquet, Ann. Inst. Pasteur (Lille), 1951, 4: 17.*—(*F. S. Lansdown*)

Hemagglutination in Leprosy.—Hemagglutination and "conditioned hemolysis" reactions were performed using sera from patients with different forms of leprosy. Comparing two antigens, tuberculin I. P. 48 and its polysaccharide fraction, the percentage of titers greater than 1:8 were, respectively: in lepromatose forms, 96.8 and 98.2 per cent with hemagglutination and 81.8 per cent with conditioned hemolysis; in tuberculoid and indeterminate forms, 56.5 and 60.8 per cent with hemagglutination and 34.8 and 47.8 per cent with hemolysis. The levels of hemagglutination or hemolysis were much higher than those obtained with sera from tuberculous patients. The differences in degree of positivity between lepromatous forms and tuberculoid or indeterminate forms seemed marked enough to distinguish the different clinical forms serologically. Hemagglutination and conditioned hemolysis reactions might be used to check the efficacy of therapy. In any event, further research should determine the value of the reactions in this respect. They constitute in the study of leprosy a new application of the antigenic relationship between *Mycobacterium tuberculosis* and *Mycobacterium leprae* (Authors' summary).—*Les réactions d'hémagglutination et d'hémolyse conditionnée dans les différentes formes de la lèpre, leur intérêt dans le diagnostic, la classification et le prognostic, C. Gernez-Rieux, E. Montestruc, & A. Tacquet, Ann. Inst. Pasteur (Lille), 1951, 4: 3.*—(*F. S. Lansdown*)

Gas Absorption During Atelectasis.—Experiments were designed to simulate the early phase of atelectasis in order to study quantitatively the rate of gas absorption from an occluded lung. Under these conditions the rate of gas absorption could be varied more than 60-fold by alteration of the partial pressures of the blood gases as well as by changes in the initial gas composition. Analyses of the composition of the alveolar gases in the occluded lobe indicate that the state of constant composition is quickly attained. This allows one to set up equations which relate the rate of gas absorption to the blood flow, pressure difference, and equivalent absorption coefficient of the various gases concerned (Authors' summary).—*Rate of gas absorption during atelectasis, W. A. Dale & H. Rahn, Am. J. Physiol., September, 1952, 170: 606.*—(*G. C. Leiner*)

Unilateral Nitrogen Breathing.—In 11 dogs under chloralose-morphine anesthesia, the

chest was opened and each lung ventilated by a separate Starling pump. Blood flow through each lung was determined by the Fick principle, both during bilateral oxygen breathing and during unilateral nitrogen breathing; the other lung received oxygen. Vascular resistance of each lung was calculated from the mean pulmonary artery pressure and blood flow. In all but 3 animals there occurred a reduction of 16 to 68 per cent of the original fraction of total flow to the nitrogen lung. The maximal effect was already present after twenty-five minutes and was promptly reversible on return to bilateral oxygen. Resistance in the nitrogen lung increased by factors of 1.3 to 4.5; in the oxygen lung it remained essentially unchanged. Oxygen saturation of the blood draining the nitrogen lung ranged from 10 to 50 per cent (equivalent to oxygen tensions of 8 to 25 mm. of mercury); of the mixed arterial blood, from 62 to 96 per cent (Author's summary).—*Effect of unilateral nitrogen breathing upon pulmonary blood flow, R. M. Peters & A. Roos, Am. J. Physiol., October, 1952, 171: 250.*—(*G. C. Leiner*)

Pulmonary Embolism.—Angiocardiograms were made of the pulmonary arteries and right heart of dogs following pulmonary embolization resembling that occurring in man. Death occurred as a result of the embolus in 2 of 6 experiments. The clots used as emboli were of such a size as to lodge in tertiary, lobar, or segmental branches of the pulmonary artery and were identifiable as filling defects or sites of occlusion in the affected vessels. In most cases the occlusion produced in a pulmonary artery by a blood clot was not complete, blood passing the clot more slowly and in reduced quantity. This fact offers an explanation for the rare occurrence of pulmonary infarction following minor pulmonary embolization, in the absence of passive congestion, in man. In 4 of 5 dogs, definite dilatation of the pulmonary arteries appeared within thirty seconds and lasted throughout the short period of observation. Vascular constriction could not be identified on the angiocardiograms. Marked, reversible dilatation of the heart appeared in one animal. In one animal which died from embolization, moderate cardiac dilatation occurred.—*Pulmonary embolism, R. P. Lochhead, D. J. Roberts, Jr., & C. T. Dotter, Am. J. Roentgenol., October, 1952, 68: 627.*—(*T. H. Noehren*)

Respiratory Effects of Salicylates.—The effect of orally and intravenously administered salicylate on respiration in the human subject has been studied by means of a Knipping-type closed circuit spirometer. In addition to an increase in depth of respiration, the drug caused a marked and progressive increase in oxygen consumption. It is suggested that this latter effect may be of fundamental importance in the therapeutic action of the drug (Author's summary).—*The respiratory effects of salicylate, J. B. Cochran, Brit. M. J., November 1, 1952, No. 4791: 964.*—(*E. A. Riley*)

Relative Effectiveness of Antihistamine Drugs.—Attempts to evaluate quantitatively the effectiveness of antihistaminic drugs are limited in the laboratory by variability of the amounts of antigen and antibody required to produce anaphylactic shock and, in clinical practice, by the variable state of the patient. The authors induced "microshocks," or nonfatal manifestations of acute dyspnea, considered analagous to acute asthma in man, when guinea pigs were sensitized to egg albumin and later exposed to aerosolized solutions of this antigen. The same animal could be used for several microshock exposures. Responses to graded doses of various antihistaminic agents could be determined. The results were in approximate agreement with those previously published by Feinberg *et al.* In terms of doses tolerable for man, the highest degree of protection was found with promethazine (Phenergan), mepyramine (Neoantergan, Anthisan), and Chlor-Trimeton, in the order named. Tripelennamine (Pyribenzamine) and diphenyhdramine (Benadryl) achieve the same high protection only with

doses toxic for man. Antazoline (Antistine), chlorcyclizine (Histantin), atropine, procaine, and procaine amide do not give comparable protection, regardless of dosage. Preliminary experiments with a new drug, BW 295/C, 51, revealed greater protection with smaller dosage than any of the others tried. Variable responses among individual animals were analagous to the situation in man. These drugs protected by counteracting mucosal edema as well as by counteracting bronchospasm.—*The protective action of antihistamines in the anaphylactic microshock of the guinea-pig, P. Armitage, H. Herxheimer, & L. Rosa, Brit. J. Pharmacol., December, 1952, 7: 625.—(A. A. Cohen)*

PUBLIC HEALTH AND EPIDEMIOLOGY

Sanatorium Treatment.—Certain trends in the sanatorium treatment of tuberculous patients were evident during the years 1946 to 1950, inclusive. There was no striking change in the extent of tuberculous disease on admission. A significant but slight increase in the percentage of patients with extrapulmonary tuberculosis only was due to the greater use of sanatoriums to treat such patients. Approximately 30 per cent of the patients admitted to sanatoriums in Ontario during 1946 to 1950 had far advanced pulmonary tuberculosis on admission. Up to the age of thirty years, more women than men were admitted; above the age of thirty-five years, more men were admitted and the excess of men increased with age. During the five-year period, artificial pneumothorax, intrapleural pneumolysis, and phrenic nerve operations were used with decreasing frequency. Streptomycin, later combined with *p*-aminosalicylic acid (PAS), pneumoperitoneum, thoracoplasty, and lung resection were used with increasing frequency. Artificial pneumothorax remained important at sanatoriums without surgical facilities; its limitations were known and the patients were more carefully selected for this type of treatment. Recumbent bed rest continued to be important and necessary. A significant, though not spectacular, increase in the duration of sanatorium stay occurred in proportion to the extent of the tuberculosis on admission and was longest for those with associated or complicating extrapulmonary tuberculous lesions. The average sanatorium stay was 15.5 months. The percentage of patients who died decreased from 20.4 to 12.2 per cent of the total discharged. This decrease was most marked among those admitted with far advanced pulmonary tuberculosis or with extrapulmonary tuberculous lesions. The important 15 per cent of patients discharged alive without medical consent still constitute a public health problem and probably accounted in part for the 25 per cent readmitted to sanatoriums. Ancillary services for the comfort, social care, and rehabilitation of patients have been accepted and utilized in modern therapy to prepare for post-sanatorium training or work. Even greater impetus has been given to the detection of persons with active tuberculosis, preferably in the early asymptomatic stage before gross destruction of tissue has occurred. —*Sanatorium treatment of tuberculous patients in Ontario, C. A. Wicks, Canad. M. A. J., November, 1952, 67: 446.—(E. A. Riley)*

Tuberculosis in Sweden.—The mortality from tuberculosis in Sweden reached its peak between 1871 and 1880, at which time there were 324 tuberculosis deaths per 100,000 population. In 1950 there were 22 deaths per 100,000. In fact, several provinces reported less than 15 deaths per 100,000. Not only has the death rate decreased, but the life expectancy of persons previously affected with tuberculosis now approaches the average life expectancy of the general population, 68 years. As a result, one large tuberculosis sanatorium has been entirely converted to the care of patients with rheumatism. In the province of Uppsala it has been possible to close 2 of the 3 sanatoriums previously needed. Most of the other sanatoriums have reallocated beds to the care of patients with chronic diseases other than tuberculosis.—*Die Besiegung der Tuberkulose in Schweden bald*

bevorstehend, E. Hedvall & O. Hillerdal, Ztschr. f. Tuberk., September, 1952, 101: 1.—(E. Dunner)

Corundum Smelter's Lung.—During the post-war years there has been interest in America as well as in Germany in a pulmonary disease acquired in the electrometallurgical production of corundum from bauxite. It has been called "bauxite worker's lung" or "Shaver's disease." In America, the cases occurred mainly in four plants near Niagara Falls, Ontario, Canada. Of 350 workers exposed, 35 became sick and 10 died. In addition, 46 showed early pulmonary changes roentgenographically. The exposure time averaged about six years but there was a variable susceptibility. The disease started with shortness of breath and, in 9 patients, spontaneous pneumothorax occurred. At autopsy, the lungs contained stringy fibrous masses with diffuse fibrosis in the thickened alveolar septa, which showed a cuboidal epithelial layer. The air spaces were compressed and filled with phagocytes, giant cells, and detritus. Other cases have been reported in the Rhineland, Germany, where 15 disabilities with 8 deaths were observed. The working time at the furnaces was six to sixteen years, but death in several cases occurred within one or two years. Active tuberculosis was found in more than half of the fatal cases, a complication not reported in the American literature. It has been suggested that "corundum smelter's lung" is pulmonary fibrosis similar to that found in aluminum workers, but no free aluminum is present in the corundum process. It is doubtful that the small amount of α-alumina in the smoke from corundum furnaces could cause the corundum smelter's lung. Mullite and amorphous silica seem to be the substances which produce this disease. Recent animal experiments with fine amorphous silica and reports of injury in the production of ferrosilicon ("pancheri"), in which the importance of amorphous silica has been stressed, implicate the latter substance as the main etiologic factor and mullite as a contributing agent.—*Etiology of corundum smelter's lung (bauxite worker's lung, Shaver's disease), H. Gärtner, A. M. A. Arch. Indust. Hyg. & Occup. Med., October, 1952, 6: 339.—(T. H. Nochren)*

Preservation of BCG.—A new method of preserving BCG vaccine uses as adjuvant a combination of 15 per cent lactose, asparagine, buffered salts, and glycerin. The product is chalky white, powdery, contains 0.5 per cent moisture or less, and is readily resuspendable. Stored at refrigerator temperatures of 4° to 6° C., it retains its viability to a high degree for periods of twelve to twenty months. At room temperature it retains its viability to a high degree for two to three months and at incubator temperatures for one to two months. Conversion of the tuberculin reaction in animal and man compares favorably with the fresh liquid vaccine except for a delay. In newborns, universal conversion occurs at twenty-eight days for the fresh as compared with fifty-eight days for the freeze-dried vaccine. Preliminary studies in guinea pigs indicate that the degree of immunity produced by the preserved vaccine equals or is better than that produced by the fresh. Virulence, pathologic, and morphologic studies indicate that the freeze-dried vaccine is in all respects similar to the freshly prepared one (Author's summary).—*The preservation of BCG by freeze-drying, S. R. Rosenthal, Acta tuberc. Scandinav., 1952, 26: 106.—(K. T. Bird)*

BCG for Contacts.—Experience with BCG in Montreuil since 1948 shows that: (*1*) A child with familial exposure to tuberculosis should be vaccinated with BCG if the general health is good, the tuberculin test is negative at 1x100, and the chest roentgenogram reveals no abnormal findings; (*2*) in such children, BCG does not activate a hypothetical latent tuberculosis nor does BCG ac-

quire any particular virulence; (*3*) in BCG-vaccinated contacts, the incidence (less than 1 per cent) and benign character of "*Beccgite*" are the same as in persons separated from the source case; (*4*) in these exposed children with negative tuberculin reactions, BCG has been proved statistically to increase the chances of antituberculous immunity; (*5*) whatever reasons account for the lack of allergy in persons in persistent contact with a massive source of infection, BCG vaccination provides additional antigen which is probably useful and in any event, harmless; (*6*) the only danger may reside in the association of antituberculous vaccination with other vaccinations. As a general rule, BCG should be given at least three months after the usual vaccinations or precede such vaccinations by six months (Authors' summary).—*Vaccination par le BCG de 82 sujets in milieu familial tuberculeux et non-séparés du contage, M. Fourestier, A. Blacque-Belair, & Mlle. R. Robert, Presse méd., November 22, 1952, 60: 1602.*—(*V. Leites*)

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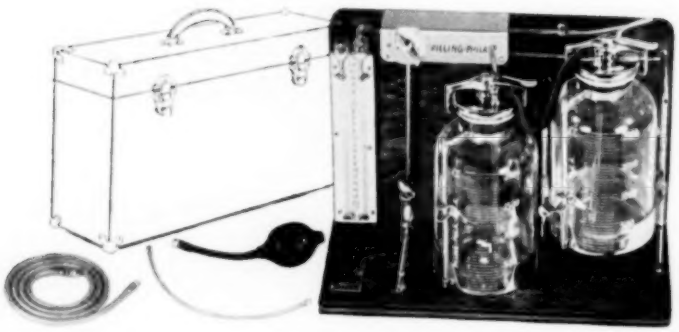

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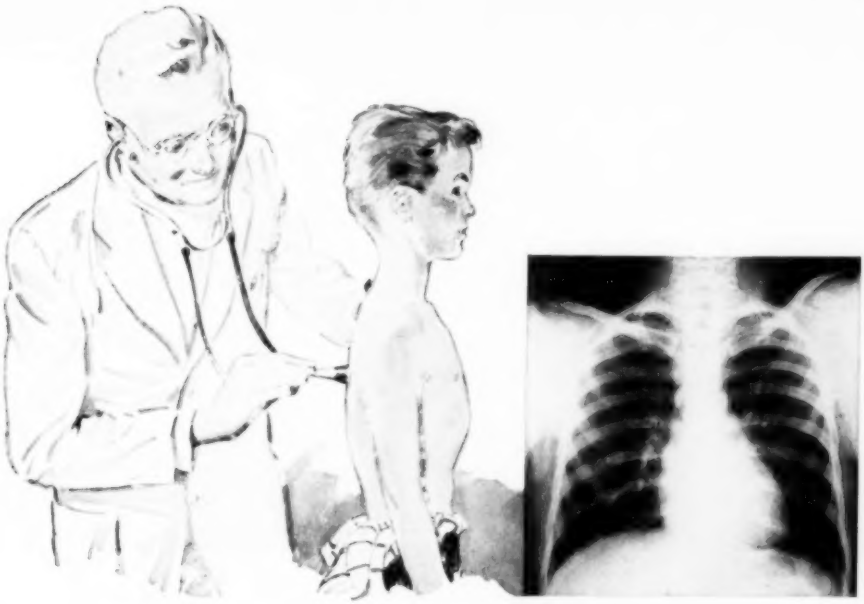

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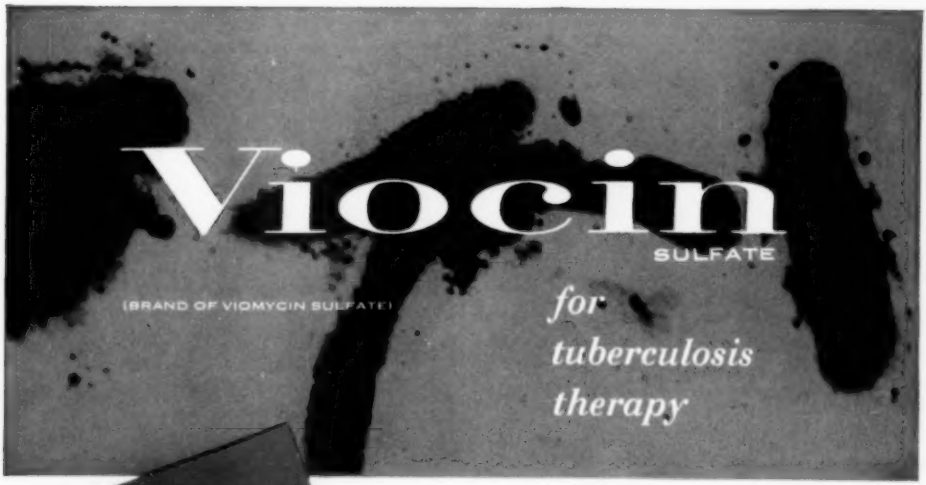

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Potassium penicillin G, units	—	100,000	100,000	—

(All supplied in 1 and 5 dose vials)

'Distrycin' and 'Dicrysticin' are registered trademarks; 'Distrycillin' is a trademark.

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a leader in the research and manufacture of penicillin and streptomycin

POSITIONS AVAILABLE

STAFF PHYSICIAN WANTED—180 bed tuberculosis hospital. American graduate only, eligible for Michigan license. Salary $7,500 to $10,000, depending on qualifications and experience. Address Box 139A, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

STAFF POSITIONS—Open at state tuberculosis sanatorium in Pacific Northwest for general or special physicians. Give full qualifications, training, etc. Box 108, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

WANTED—Staff physician in approved tuberculosis hospital. Must be a citizen and eligible for California license. $484 to $595 per month. Single or family maintenance at nominal charge. Address: Superintendent, Arroyo Del Valle, Livermore, Calif.

WANTED—Resident physician in approved tuberculosis hospital. Must be a citizen and eligible for California license. One- or two-year residency. $200, $413 or $575, depending on qualifications of applicant. Single or family maintenance at nominal charge. Address: Superintendent, Arroyo Del Valle, Livermore, Calif.

WANTED—Asst. medical director for 225 bed tuberculosis sanatorium, near Chicago. New home available for family. Excellent salary. Apply, Superintendent, Parramore Hospital, Crown Point Ind.

WANTED—Staff physician for approved county tuberculosis hospital, American citizenship and Ohio license necessary. Attractive salary. Box 118, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

SUPERINTENDENCY of a 200 bed tuberculosis hospital in large midwestern city available July 1st. Four bedroom house available. Salary commensurate with qualifications. Box 119, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

TUBERCULOSIS—Resident and assistant residents for new 440 bed division of large general hospital. Complete medical, surgical, and pathological facilities. Excellent training program, medical school affiliation. East coast city. Box 120, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

PHYSICIANS—full time, for new 440 bed tuberculosis division of large general hospital. Associated with two medical schools for teaching purposes; opportunity for research. Complete medical, surgical, and pathological facilities. There is a house staff including rotations from general hospital staff. Salary governed by background of training and experience. Box 121, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

WANTED:—Medical director, tuberculosis experience essential. Attractive salary, modern home, hospital approved by American College of Surgeons. The hospital is Kalamazoo County owned and has 50 beds for tuberculosis, 12 beds for county convalescent cases (female only), and 19 beds for contagious cases. Make application read attention Chairman, Board of Trustees, Fairmount Hospital, Kalamazoo, Mich.

POSITIONS WANTED

ASSISTANT HOSPITAL ADMINISTRATOR—Over ten years' administrative work, including last seven in both voluntary and official health agencies; hospital survey experience; heavy on personnel management. Graduate training in administration. Age 40; married, three children. Box 122, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

BOARD MAN INTERNAL MEDICINE—Sub-spec. chest diseases, single, 44 years, excellent health, draft exempt, 20 years' experience in pulmonary tuberculosis, 10 years Director and Superintendent of State TB Sanatoria, Director of Control of TB, excellent references, wants position in New York State or state recognizing New York State license. Prefer directorship in county sanatorium, would consider association with internist or chest specialist or buy established specialty practice in New York City. Box 123, American Review of Tuberculosis, 280 Madison Ave., N. Y. 16, N. Y.

BACK ISSUES Urgently Needed

The American Review of Tuberculosis will pay $1.00 each for any of the following issues in good condition:

January 1949	January 1951
February 1949	February 1951
March 1949	January 1952
July 1949	March 1952
November 1949	August 1952

September 1952

W W W

Send promptly with covering bill to:

AMERICAN REVIEW OF TUBERCULOSIS

1790 Broadway **New York 19, N.Y.**

NATIONAL TUBERCULOSIS ASSOCIATION

ANNUAL MEETING **MAY 18-22, 1953**

LOS ANGELES, CALIFORNIA

The annual meeting of the National Tuberculosis Association will be held in Los Angeles, California, May 18-22, 1953. The Hotel Statler and the Biltmore Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a twin bed room if possible.

Application for room reservations should be made directly to the hotel of your choice.

HOTEL	ADDRESS	SINGLE	TWIN	SUITES
Alexandria	210 W. 5th Street	$4.00- $8.00	$7.00-$10.50	$12.50-$25.00
Biltmore	515 S. Olive Street	$7.00-$11.50	$10.50-$14.50	$17.00-$33.00
Clark	426 S. Hill Street	$4.00- $6.00	$6.00-$ 8.00	$12.00-$18.00
Commodore	1203 W. 7th Street	$3.50-up	$6.00-up	$10.00-up
Hayward	206 W. 6th Street	$4.00- $6.00	$6.50- $8.00	$9.00-$15.00
Lankershim	230 W. 7th Street	$3.50- $5.00	$6.00- $7.50	$10.50
Mayfair	1256 W. 7th Street	$4.50-up	$7.50-up	$17.50
Mayflower	535 S. Grand Avenue	$5.25- $8.00	$5.75- $9.00	$14.00
Ritz Flower	813 S. Flower Street	$4.00- $5.00	$5.00- $6.00	—
Savoy	601 W. 6th Street	$4.00- $5.00	$5.50- $6.50	$8.00- $8.50
Statler, Wilshire and Figueroa		$6.50-$14.00	$10.00-$20.00	$19.00-$34.00

IMPORTANT ANNOUNCEMENT

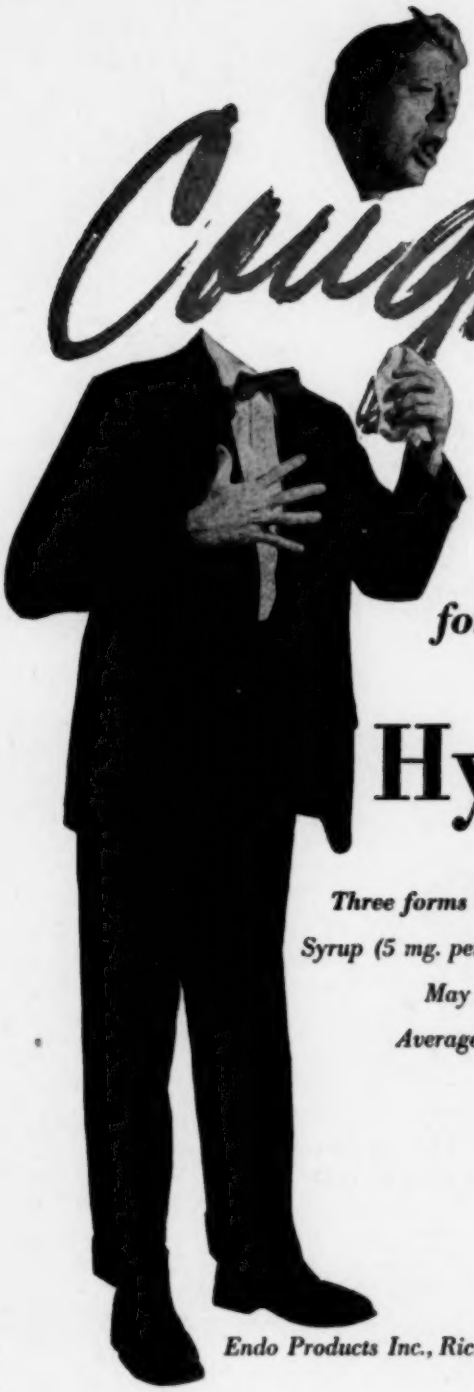
THE AMERICAN REVIEW OF TUBERCULOSIS has made available to its readers a section devoted to classified advertising pertaining to positions available and wanted. Since there have been so many requests for this type of service in the tuberculosis field, the Editorial Board of THE AMERICAN REVIEW OF TUBERCULOSIS decided to include a classified section at a nominal charge for each entry.

- Cost per advertisement of 25 words or less will be $3.50, additional words 15 cents each.
- Bold Face Semi-display will be $5.00 per insertion for 25 words or less, additional words 20 cents each.
- Post Office Box numbers will be an additional 75 cents per advertisement.
- Address all classified advertisements, with check or money order enclosed, to:

THE AMERICAN REVIEW OF TUBERCULOSIS

280 MADISON AVENUE **NEW YORK 16, N. Y.**

Murray Hill 5-8140



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(Dihydrocodeinone Bitartrate)

Three forms available: Oral Tablets (5 mg. per tablet), Syrup (5 mg. per teaspoonful), Powder (for compounding).

May be habit forming; narcotic blank required.

Average adult dose 5 mg. Literature on request.

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